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CHILDHOOD MOTOR DEVELOPMENT AND LEISURE-TIME PHYSICAL ACTIVITY IN YOUNG ADULTHOOD: A DISCORDANT TWIN-PAIR ANALYSIS

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Introduction: Previous longitudinal studies have shown that the motor proficiency in early life may act as a determinant of physical activity in later life. However, familial factors including genetic effects may explain the association, but long-term follow-up studies taking into account potential confounding by family background are still missing. The study design of discordant same-sex twin pairs enables adjustment for genetic, familial and other factors shared by co-twins. The aim of the present twin study was to investigate whether the parental reports of within-pair differences in childhood motor skill development are associated with self-reported leisure-time physical activity levels in young adulthood independently of familial background. *Materials and Methods:* Participants were identified from two ongoing Finnish twin studies, the FinnTwin12 and FinnTwin16 studies. 1,550 twin pairs (795 MZ, 755 same-sexed DZ) from the FinnTwin12 study and 1,752 twin pairs (882 MZ, same-sexed 871 DZ) from the FinnTwin16 study with the relevant variables were included in the analysis. Childhood motor development was assessed by questionnaire sent to the parents at baseline (age 11 for FinnTwin12 and age 16 for FinnTwin16). Parents reported whether one or the other of the co-twins had been ahead in motor skill development in infancy and childhood. The motor skill development indicators assessed were: (1) turning over from back to stomach, (2) standing unaided, (3) walking unaided, (4) climbing stairs unaided, (5) general motor skills at age 6 years, (6) agility in childhood and (7) physical strength in childhood. Leisure-time physical activity was assessed at wave 4 of each study, when the twins were young adults (mean age 24.4 years, *SD* 1.3 years, range 19–28). Leisure-time physical activity was based on questionnaire data, and the activity level was assessed as leisure-time MET hours/day. The associations between the pairwise differences in childhood motor development indicators and pairwise differences in leisure-time physical activity levels in young adulthood were analyzed using conditional linear regression analysis. *Results:* In both cohorts, learning to stand unaided earlier in infancy predicted higher leisure-time MET values in young adulthood (FinnTwin16 $p = .001$ and FinnTwin12 $p = .02$). In the FinnTwin16 study sample, having been ahead in climbing stairs unaided ($p = .04$), in agility ($p = .02$) and in general motor skills ($p = .005$) in childhood also predicted higher leisure-time MET values as young adults. A similar tendency was seen for childhood agility in the FinnTwin12 study sample but the difference was not statistically significant in this sample. The co-twins who had been ahead in walking unaided in infancy had statistically significantly higher leisure-time MET values in young adulthood according to the FinnTwin12 study sample ($p = .05$). However, this association was not seen in the FinnTwin16 study sample. The significance of the associations were robust to adjustment for birth weight and birth order with the exception of with the indicator 'standing unaided' in the FinnTwin12 cohort. *Conclusion:* More advanced childhood motor development is associated with higher leisure-time MET values in young adulthood at least partly independently of familial background. Motor skill interventions to improve movement skills of preschool children may be effective in promoting long-term physical activity.

HERITABILITY OF LOWER URINARY TRACT SYMPTOMS IN MEN

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Introduction: Urinary conditions such as urinary incontinence, overactive bladder, and chronic prostatitis/chronic pelvic pain syndrome are common, comorbid, disabling, and without clear etiology. Common to all of these conditions are non-specific urinary symptoms such as urgency and frequency, known as Lower Urinary Tract Symptoms (LUTS). LUTS are associated with significant negative impact on quality of life and economic burden, and increase with advancing age. However, little is known about the etiology of LUTS and the relative contribution of genetic and environmental factors to the phenotypic variance of LUTS. To date, only one study has examined the heritability of LUTS in women, finding robust evidence of a genetic influence for susceptibility to urinary incontinence, frequency and nocturia, but also that shared environmental factors seem important for the predisposition to develop overactive bladder. No similar studies have focused on heritability of LUTS in men. *Materials and Methods:* The aim of this study was to examine the relative contribution of genetic and environmental factors to the phenotypic variance of LUTS in men. Data from the Vietnam Era Twin Registry

were used to address this aim. Male health conditions were assessed by a mail health survey that included the International Prostate Symptom Score (I-PSS), an 8-item validated self-report measure of LUTS. Biometric modeling was used to evaluate the genetic and environmental contribution to variance for LUTS. *Results:* The sample consisted of 1,002 monozygotic (MZ) and 580 dizygotic (DZ) male twin pairs. Participants were middle aged adults (mean age = 50.2 years; *SD* = 3 years) and predominantly Caucasian (94.3%). Nearly 25% of the entire sample had an I-PSS score > 8 which is indicative of at least moderate LUTS and is consistent with prevalence in the community. The best fitting models for the symptoms of incomplete emptying, frequency, urgency, weak stream, and nocturia included additive genetic and non-shared environmental effects; the models for intermittency and straining included additive genetic, shared environment, and non-shared environment. Heritability estimates ranged from 21% (nocturia) to 37% (intermittency), with moderate heritability (34–36%) for the frequency and urgency symptoms. *Conclusion:* Understanding the heritability of these symptoms is important to elucidating the underlying contributing factors to urinary conditions with unclear or overlapping etiology. We found a moderate contribution of genetic factors to the phenotypic variance of LUTS, suggesting that environmental factors may contribute substantially to these symptoms in men. Future research can further examine specific biological mechanisms and environmental factors that contribute to the development of conditions with LUTS.

CANCER RISK IN OPPOSITE-SEXED TWINS

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Introduction: There is increasing evidence that some types of cancer originate in utero, particularly hormone-related cancers. Twin pregnancies are characterized by higher levels of pregnancy estrogens than singleton pregnancies. According to the maternal estrogen hypothesis, elevated exposure to prenatal estrogen may increase the risk of adult cancers, especially breast and testis cancer. Moreover, testosterone is suggested to play a role in hormone-related cancers, and animal studies have shown that exposure to testosterone is influenced by the intrauterine fetal position. The twin testosterone transfer hypothesis reflects the possibility that human sex hormones can transfer from one twin to the other, and some evidence exist of higher testosterone levels in utero for opposite-sex (OS) compared with same-sex (SS) female twins. *Materials and Methods:* Using high quality registry data from NORDCAN, a database with registrations of cancer incidence and mortality in the Nordic countries, we compared cancer incidence for OS (n = 92,642) and SS (n = 205,101) twins born in Denmark and Sweden during 1870-2004. The observational period started in 1943 in Denmark and in 1962 in Sweden. A total of 29,301 cancers were observed among 26,935 individuals, including 9,539 cancers of the breast, corpus uteri, ovary, prostate, and testis. By calculating standardized incidence ratios (SIRs) and 95% confidence intervals (CIs), observed cancers in OS and SS twins, respectively, were compared to the expected numbers based on sex, country, tumour type, calendar period, and age-specific incidence rates in the general population, thus showing cancer incidence between twins and singletons. The incidence rate ratios (IRRs) were the SIRs for OS divided by the SIRs for SS twins, and 95% CIs were investigated using a Poisson regression adjusted for dependence within twin pairs. *Results:* We found that risk of breast cancer was similar in female twins and singletons, whereas twins had a slightly lower risk of cancer of corpus uteri and ovary. The SIRs (95% CIs) were 1.02 (0.99;1.05) for breast cancer, 0.92 (0.86;0.98) for corpus uteri cancer, and 0.92 (0.86;0.99) for cancer of ovary and uterine adnexa. Male twins had a slightly higher risk of prostate cancer than singleton males before the age of 70, SIR = 1.09 (1.04;1.14), but similar incidence was found for testicular cancer. For cancer at all sites, a slightly lower risk was found for twins than singletons of both sexes. The SIR was 0.96 (0.95;0.98) for females and 0.95 (0.93;0.97) for males. No significant differences in cancer incidence were found between OS and SS twins neither for hormone-related cancers nor cancers at all sites. However, an indication of an increased risk of corpus uteri cancer among premenopausal OS than among SS female twins was found, IRR = 1.55 (0.98;2.47) — possibly a result of multiple testing. *Conclusion:* The present study found no evidence for the maternal estrogen hypothesis; however, a slight effect of estrogen exposure in utero on prostate cancer risk cannot be excluded. In addition, no strong impact of possible elevated prenatal testosterone exposure on cancer incidence was found. The results support that twinning per se is not a risk factor of cancer.

IS THE SEQUENTIAL LASER TECHNIQUE FOR TWIN-TO-TWIN TRANSFUSION SYNDROME TRULY SUPERIOR TO THE STANDARD SELECTIVE TECHNIQUE? A META-ANALYSIS

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Introduction: Sequential selective laser is an adaptation of the selective technique for the treatment of twin-to-twin transfusion syndrome (TTTS) whereby anastomoses are coagulated in a specific order. The theoretical benefit is to obliterate the anastomoses in a sequence that allows, at least partly, an intraoperative correction of the hypoperfusion of the donor and hyperperfusion of the recipient. This study aimed to investigate the efficacy of sequential laser coagulation. *Materials and Methods:* MEDLINE, Embase and the Cochrane library were systematically searched for comparative studies on the efficacy of sequential versus standard selective laser coagulation for TTTS. The primary outcome measure in these studies was survival of at least one twin, both twins and fetal demise. *Results:* Three cohort studies comparing selective laser treatment technique (n = 120) versus sequential technique (n = 224) in 344 monochorionic twin pregnancies were included. Mean survival of at least one twin was 88% in the selective group versus 92% (p = .22) in the sequential group. Mean survival of both twins was lower in the selective group (52%) than in the sequential group (75%) (p = .002). Donor fetal demise decreased from 34% in the selective to 10% in the sequential group (p < .01), recipient fetal demise decreased from 16% to 7% (p = .02). *Conclusion:* Limited evidence suggests improved double neonatal survival as well as decreased donor and recipient fetal demise with the use of the sequential technique. However, these results are based on small non-randomized studies with evident forms of bias and methodological limitations. A randomized controlled trial to assess the efficacy of sequential laser technique is therefore required.

ASSOCIATION BETWEEN SNUS USE IN ADOLESCENCE AND CIGARETTE SMOKING IN EARLY ADULTHOOD - A PROSPECTIVE STUDY AMONG FINNISH TWINS

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Introduction: Snus, the Swedish variety of oral moist snuff, is a form of smokeless tobacco. The selling of snus is banned in Finland since 1995, but imports for personal use from Sweden and 'under the counter' sources have contributed to maintain this habit in the Finnish population, with young males at highest risk. It is under debate whether the use of smokeless tobacco products may represent a gateway to later cigarette smoking. We investigated the association between snus use in adolescence and cigarette smoking in early adulthood among Finnish twins. *Materials and Methods:* Data on snus use and cigarette smoking were obtained from waves 3 (mean age 17) and 4 (mean age 22) of the population-based FinnTwin12 cohort, including 2,938 participants, with information on tobacco use in both waves. At wave 3, a mailed questionnaire inquired about current smoking habits and lifetime snus use. We categorized individuals as non-smokers at baseline if they had never smoked or had quit smoking. At wave 4, the participants were categorized according to their smoking status as current smokers (daily or occasional) or non-current smokers. We analyzed the twins as individuals. Because the twins were sampled as clusters, the primary unit being the twin pair, the clustering of correlated observations from twin pairs was controlled for when computing standard errors of the estimates using robust estimators of variance. *Results:* At wave 3, 1,951 participants were non-smokers. Of them, 256 (13%) had tried snus (22% boys, 5.8% girls). Among those non-smokers at baseline who had tried snus, 6.5% had used it once, 5% 2–50 times, 1% more than 50 times, and 0.66% were regular users. Of those non-smokers at baseline who had used snus, 33.6% were current cigarette smokers at follow-up, compared to 13.2% among individuals who had never used snus at baseline. Among non-smokers at baseline, a logistic regression model adjusted for sex showed that the risk of being a current smoker at follow-up among adolescents who had used any snus at baseline was almost three-fold (OR = 2.73, 95% CI 1.97–3.77, $p < .001$), compared to those who had never used snus. *Conclusion:* Our results among Finnish twins suggest that snus use in adolescence may act as a gateway to cigarette smoking in early adulthood.

ARABIN CERVICAL PESSARY TO PREVENT PRETERM BIRTH IN TWIN PREGNANCIES WITH SHORT CERVIX

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Objective: To evaluate the effect of the Arabin cervical pessary in twin pregnancies with a short cervical length. *Materials and Methods:* Study design: This is a retrospective observational study in twin pregnancies with a cervical length ≤25mm between 21 and 31 gestational weeks. Patients who received an Arabin cervical pessary were compared with controls who did not receive a pessary. Cases and controls were matched for chorionicity, gestational age at admission and cervical length measurement. Clinical characteristics and pregnancy outcome of patients who underwent pessary treatment were compared to the group without treatment. Outcomes included: gestational age (GA) at delivery, delivery before and <36, 34 and 32 weeks, latency between detection of a short cervix and delivery, duration of hospital admission. A matched paired analysis was performed to compare the two groups. *Results:* The study group consisted of 30 patients with a twin pregnancy receiving a cervical pessary for short cervical length and 30 controls. Women with a pessary delivered at a higher GA compared with patients with expectant management (35 compared to 33 weeks, respectively, $p = .02$). The incidence of delivery <36 weeks was significantly lower in the group with pessary (63% vs. 93%, $p = .02$). No significant difference was found in the rate of deliveries before 32 and 34 weeks between the groups, likely due to the small sample size. For patients treated with pessary, the time interval between detection of short cervix and delivery was significantly longer (53 vs. 42 days, $p = .04$) and the duration of hospital admission was significantly shorter (13 vs. 22 days, $p = .02$) compared to controls. *Conclusion:* Our pilot study, the use of Arabin cervical pessary significantly prolonged gestation and reduced the incidence of delivery <36 weeks. It was also associated with a lower number of days of hospital stay and hence with lower costs.

CAUSES OF CO-OCCURRING SOMATIC, ANXIOUS, AND DEPRESSIVE SYMPTOMS IN ADOLESCENTS

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Introduction: Earlier studies exploring the nature and etiology of a latent internalizing factor as an explanation for co-occurring distress symptoms in adolescents usually focus upon the relationship between anxious and depressive symptoms. It is unclear how medically unexplained somatic symptoms will relate to this underlying factor and its etiology. Based on the classical twin design with monozygotic and dizygotic twins reared together, our study aimed to explore the relative importance of genetic and environmental factors for the covariance of somatic, anxiety, and depression symptoms in adolescent girls and boys. *Materials and Methods:* A population-based sample of twins aged 12–18, their mothers and their fathers ($N = 1,394$ families) responded to questionnaire items measuring the three phenotypes. Informants' ratings were collapsed using maximum likelihood estimated factor scores. Multivariate genetic analyses were conducted to examine the etiological structure of co-occurring somatic, anxiety, and depression symptoms. *Results:* Our results confirm the presence of substantial overlap among somatoform, anxiety, and depression symptoms. The best fitting model was an ACE common pathway model without sex limitation with one substantially heritable (44%) latent internalizing factor shared by the three phenotypes. Co-occurring symptoms also resulted from shared (25%) and non-shared (31%) environment. The factor loaded most on the depression symptoms, and least on the somatic symptoms. All phenotypes were also affected by genetic influences specific to each. Trait-specific influences explained 44% of depression variance, 59% of anxiety variance, and 65% somatic variance. *Conclusion:* Our results suggest the presence of a general internalizing factor along which anxiety, depression and somatic symptoms can be modeled, sharing etiological components. However, significant unique influences make the symptoms types distinguishable.

TWINS WITH DISCORDANT BIRTH WEIGHT: ANTHROPOMETRIC, HORMONAL AND METABOLIC FOLLOW-UP DURING THE FIRST TWO YEARS OF LIFE

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Introduction: Intrauterine growth restriction (IUGR) has been associated with an increased risk of health problems later in life. In twin pregnancies discordance in birth weight can occur. It has been argued that twins with lower growth than singletons could represent a natural model of IUGR. So far, there are few studies on the monitoring of discordant birth weight twins and on the possible health outcomes compared to those of singletons born with IUGR. *Materials and Methods:* To obtain twin-to-twin pair data and to detect early indices of adult diseases, in a matched-pair prospective cohort study, anthropometric, metabolic and hormonal data have been investigated in twins with discordant birth weight >15%. Discordance was calculated from the weight of the larger twin. Thirty twins have been followed quarterly for their first 2 years of life through anthropometric traits (weight and length). Growth parameters were assessed based on *z*-scores. At each follow-up visit, metabolic (glycaemia, total and HDL cholesterol, triglycerides, ApoA1 and ApoB) and hormonal (insulin, IGF-1, cortisol, TSH and fT4) evaluations were performed. *Results:* Growth Pattern: Length of small twins was -2*SD,* occurring in 100% of infants within the sixth month of life. Weight was regained slower and all the population reached values >-2*SD* by 2 years. In each pair of twins, a progressive trend to recover the discrepancy in weight and length has been observed. Mean weight discordance was 28.5% at birth, 14.6% at 1 month and <5% from the first year of life. In all the twin pairs the difference was <15% at 2 years. Length was found to be more similar than weight with a mean discordance of 6.6%, 1.6%, 1.3% and 0.5% at birth, 6 months, 1 and 2 years respectively. Hormonal Profile: Higher levels of TSH (in euthyroidism) and cortisol (at 6 months) have been found in IUGR/SGA with respect to AGA infants. Higher levels of IGF-1 and cortisol have been associated with catch-up growth of length and weight, respectively. Lipid Profile and Insulin Resistance: By considering the main metabolic indices (TG/HDL, ApoB/A1, I/G and HOMA-IR) IUGR/SGA did not significantly differ from AGA subjects. *Conclusion:* Our results in a series of 30 birth weight discordant twins do not seem to indicate severe auxo-metabolic-hormonal alterations during the first 24 months of life. Small twins seemed to have the same pattern of growth as IUGR babies. In these infants the monitoring of cortisol and TSH should be of interest. A longer follow-up in a larger population is necessary to confirm these preliminary data.

OBSTETRIC AND PERINATAL OUTCOMES IN MONOCHORIONIC MONOAMNIOTIC TWIN PREGNANCIES

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Introduction: To evaluate the obstetric and perinatal outcomes in a large series of monochorionic monoamniotic twin pregnancies. *Materials and Methods:* We conducted a descriptive study by reviewing the cases of monochorionic monoamniotic twin prenancies attending at our hospital between the years 1997 and 2013. 29 patients were obtained. Mean gestational age at diagnosis was 15.8 ± 4.5 weeks. Mean maternal age was 31.9 ± 3.5 years. Obstetric complications and perinatal outcomes were recorded. Data was analyzed using binary logistic regression. *Results:* In 4 cases (13.8%) invasive prenatal diagnostic techniques were performed (2 amniocentesis and 2 chorionic biopsies). There were 3 cases of fetal malformations (10.3%). Fetal transfusion syndrome was diagnosed in 1 case (3.4%). There were 10 intrauterine deaths (17.2%), 4 cases affecting both twins. In 7 patients cord entanglement was diagnosed by ultrasound (24%). In 2 of the cases of cord entanglement, the death of one twin occurred postnatally. There was premature rupture of membranes in 4 cases (13.8%) and preterm labor in 13 (45%). Inatruterine growth restriction was observed in any of the two twins in 6 cases (21%). The gestational age at delivery was 32.3 ± 6.3 weeks, 7 of them by vaginal delivery (24%), 2 of them single twins. There were four cases of neonatal deaths, with both twins affected in one patient (neonatal mortality 4/48, 8.3%). Overall perinatal mortality was 14/58 (24.1%). Binary logistic regression analysis failed to prove any correlation between the data recorded and perinatal mortality. *Conclusion:* Monoamniotic monochorionic twin pregnancies present high perinatal morbidity and mortality, although our results are better than those reported in the literature. No variable was predictive for perinatal death in our study, including cord entanglement prenatal sonographic diagnosis, even though elective delivery at 32 weeks has demonstrated reduced antenatal mortality despite prematurity.

THE GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO CORRELATIONS BETWEEN PERCEPTIONS OF FAMILY ENVIRONMENT AND ACTIVITY IN RUSSIAN ADOLESCENT TWINS

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Introduction: Gene-environment correlations have been studied in behavior genetics since the beginning of the 1980s, including the genetic influences on the perceived family environment; however, the majority of studies have been based on retrospective self-reports. The aim of the current study is to analyze the sources of variance (additive genetic factors, shared and nonshared environmental variance) in correlations between perceived family environment and activity scales of T.Achenbach's ASEBA in Russian adolescent twins. *Materials and Methods:* The perceptions of family environment were assessed by the Russian version of Family Environment Scale (Moos & Moos, 1981). The activity phenotype was assessed by the combination of youth self-report and parental report 'activities and competencies' scales of T.Achenbach's test battery (Russian version) produced using the first component of principal components analysis. The influence of genetic and environmental factors were estimated using structural equation modeling in OpenMx/R software. The sample included 466 11- to 17-year-old ($M = 14$, $SD = 2$) male (52%) and female (48%) twins from Izhevsk, Moscow and St.Petersburg in the Russian Federation. *Results:* The activity composite and the perceptions of family environment (10 FES scales) were modestly correlated on a phenotypic level. The highest genetic contribution to the correlations were between the activity composite and the Expressiveness scale, as well as with Conflict, Achievement, Independence, and Organization. The highest shared environmental contribution to the correlations were between the activity and the Intellectual-Cultural Orientation, the FES Activities scale, and

the Family Cohesion. *Conclusion:* The activity and competence as assessed by T.Achenbach's ASEBA battery and the perceptions of family environment are modestly correlated on the genetic and environmental levels in Russian adolescent twins. A bigger sample is needed to explore the possible effects of gender and pair composition.

AGGRESSION IN CHILDREN: UNRAVELING GENE-ENVIRONMENT INTERPLAY TO INFORM TREATMENT AND INTERVENTION STRATEGIES

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Introduction: Childhood aggression and its resulting social impairment inflict a huge personal and financial burden on affected children, their relatives, peers and society as a whole. ACTION brings together a strong team of European scientists who work together in this research project with colleagues from Australia and the United States, who have access to large prospective twin, population-based and clinical cohorts and who collaborate with psychiatrists, clinicians, educators and (ortho)pedagogues, and SMEs with a portfolio in biomarker and epigenetics research. ACTION aims to bridge the gap between basic science and daily practice by responding to critical needs formulated by psychiatrists and clinicians by providing a basis to match treatment strategies to children's individual risk profiles. *Materials and Methods:* ACTION aims to provide an inventory of diagnostics practices, prevention, and therapeutic interventions, and examines societal outcome of childhood aggression later in life by studying large-scale prospective population-based data. In addition, ACTION aims to unravel the causes of individual differences and the gene-environment interplay in aggression and the associated comorbidities by means of genetic epidemiology, genome-wide association (GWA) and genome-wide epigenetic analyses. ACTION will investigate the metabolomic profile of aggressive behaviour to validate biomarkers. Finally, ACTION will combine the empirical findings into a comprehensive framework and will develop risk assessment charts together with guidelines to improve decision making on the development and implementation of treatment and prevention programs. *Results:* ACTION will combine the data from pediatric twin and population cohorts to investigate the longitudinal, gender-specific, and multivariate architecture of aggression and its comorbidities. It will estimate genetic and environmental variance and covariance based on multivariate and longitudinal modeling of multiple rater (mother, father, teacher) twin data, based on SNP data (Genome-wide Complex Trait Analysis (GCTA)), and based on linkage information in dizygotic twins with SNP data. Through genetic association studies (in collaboration with replication cohorts), it will identify genomic regions of interest (genomic variants, CNVs). A selection of uniquely informative participants (discordant monozygotic twin pairs and concordant monozygotic twin pairs scoring high and low on aggression) will be made for the genome-wide epigenetic and metabolomics studies. *Conclusion:* The mission of ACTION is to develop a comprehensive framework of the causes of individual differences in paediatric aggression. This will improve the profiling of large clinical groups allowing better classification of subgroups and informing the development of individually-tailored and more effective preventive and therapeutic interventions.

AN OVERVIEW OF TWIN-FAMILY AND MOLECULAR GENETIC STUDIES INTO WELLBEING

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Introduction: In recent years, wellbeing has become a topic of research across several scientific disciplines. A major force driving this broad interest is the association of wellbeing with physical and mental health and its possible pivotal role in socio-economic issues and economic development. Previous twin-family studies have revealed that individual differences in wellbeing and its components — Satisfaction with Life, Happiness, and Quality of Life — are accounted for by both genetic as well as environmental factors but the range in estimates is large. Given the heritability estimates for wellbeing, searching for genomic regions involved in variance in wellbeing is justified. *Materials and Methods:* A systematic literature search identified 30 twin-family studies on wellbeing or a related measure such as satisfaction with life or happiness. Twelve independent heritability estimates from 10 studies were meta-analyzed, by computing the weighted average heritability, to estimate broad-sense heritability for wellbeing, and 9 heritability estimates, derived from 9 independent samples, were used for the meta-analysis of satisfaction with life. In addition I will provide an overview of all existing molecular genetic studies involving wellbeing. *Results:* The weighted average heritability of wellbeing was 41%, while the weighted average heritability for satisfaction with life was 36%. With this result a more accurate estimate of the relative influence of genetic effects on wellbeing is provided. So far, there have been only a few attempts to find genetic polymorphisms associated with wellbeing, showing mixed results. The only genome-wide linkage study found two suggestive linkage peaks on chromosome 1 and 19 associated with happiness (Bartels et al., 2010). In addition, one study reported an association of life satisfaction and the more efficient VNTR polymorphism on the serotonin transporter gene (5-HTTLPR), but replication failed (De Neve, 2011; De Neve et al., 2012). A second candidate gene study found a significant association between happiness and the less efficient VNTR polymorphism on the monoamine oxidase-A (MAOA) gene in women, but not in men (Chen et al., 2013). Finally, a small study found that leukocyte basal gene expression profiles were different between hedonic and eudaimonic well-being (Fredrickson et al., 2013). Using whole-genomic data, it was estimated that the fraction of variance explained by all single-nucleotide polymorphisms (SNPs) in subjective wellbeing (SWB) was 12–18% after correction for measurement error (Rietveld et al., 2013). A large (~150 k) genome wide association meta analysis on SWB will appear in the beginning of 2015. *Conclusion:* The twin-family study meta-analysis provided a more accurate estimate of the relative influence of genetic effects on wellbeing. The results of the few studies that have attempted to find genetic polymorphisms associated with subjective wellbeing are showing mixed results. The significant finding of genetic influences on wellbeing based on whole genomic SNP arrays, the upcoming GWAS on wellbeing and our increasing knowledge to obtain more information from genomic data suggest optimism about the prospect for using genetic data in subjective wellbeing.

OVERLAP BETWEEN WELLBEING AND MENTAL ILLNESS THROUGHOUT THE LIFESPAN

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Introduction: Promotion of mental wellbeing and prevention of mental illness are suggested to go hand in hand. Prevention of mental illness is of increasing urgency given the wide-ranging individual, societal, and economic impact of these disorders (World Health Organization, 2004, 2010). The value of promoting wellbeing in conjunction with prevention of mental illness depends in part on the sources of overlap between SWB and mental illness. *Materials and Methods:* The present study examined the association between wellbeing, a factorscore derived from the satisfaction with life scale, the subjective happiness scale and a measure for quality of life, and mental illness. Mental illness is assessed with age-appropriate surveys of the Achenbach taxonomy. Data on wellbeing have been collected from early childhood (parental report at ages 3, 7, 9, 12), to adolescence (self-report at ages 14 and 16) and late adulthood (self-report from ages 18–100). Cross-sectional and longitudinal multivariate analyses will be conducted in a genetically informative twin-sibling design to unravel the sources of overlap between wellbeing and mental illness. *Results:* Significant associations between wellbeing and internalizing problems have been found but wellbeing is also significantly associated with exernalizing behavior. The genetic analyses will provide insight into the underlying sources of overlap. *Conclusion:* Wellbeing and mental illness are associated. This association is partly based on overlapping genetic factors. The less than perfect overlap reflects the innovative approach of mental illness prevention via wellbeing promotion.

THE GLASS IS HALF FULL AND HALF EMPTY: OPTIMISM AND PESSIMISM AS DISTINCT SYSTEMS WITH MULTIPLE BIOLOGICAL INFLUENCES

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Introduction: Optimistic and pessimistic beliefs are linked to outcomes including health and depression. Yet it is unclear if these apparent opposites form a single dimension or two distinct systems. The extent to which personality accounts for differences in optimism/pessimism is also controversial. Here, we used a genetically informative sample to answer these questions. *Materials and Methods:* 852 pairs of US midlife twins were administered both the optimism and pessimism scales of the life orientation scales, and the 5-factor personality inventory. *Results:* Optimism and pessimism showed distinct pathways of genetic influence as well as significant genetic links to four of the five major personality domains.Genetic variance in optimism largely reflected emotional stability and extraversion. Pessimism shared (reversed) influences from these traits, but conscientiousness and agreeableness uniquely decreased pessimism. Both optimism bias and pessimism showed genetic variance distinct from all effects of personality. The specific genetics of optimism acted to implement a good-news bias. Genetic effects restricted to pessimism may underlie associations of pessimism to depression. *Conclusion:* Both optimism bias and pessimism showed genetic variance distinct from all effects of personality. The specific genetics of optimism acted to implement a good-news bias. Genetic effects restricted to pessimism may underlie associations of pessimism to depression.

NATION-WIDE COMPARISON OF PERINATAL OUTCOME OF INDUCED VERSUS NATURAL TWINS IN THE NETHERLANDS 2000-2012

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Introduction: Since the introduction of ovulation induction (OI), intra-uterine insemination (IUI) and in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) the incidence of multiple pregnancies has increased. The twinning rate after IVF is 20% to 40%, after IUI and OI it is 10–15% compared with approximately 1% following natural conception (NC). Multiple pregnancies are a concern; they are associated with adverse perinatal and maternal outcomes. Also, singletons conceived after IVF, ICSI, IUI or OI have worse perinatal outcomes compared with naturally conceived singleton pregnancies. Literature comparing pregnancy outcomes in natural and artificially induced multiple pregnancies have been contradictory. We compared pregnancy outcome of natural DZ twin pregnancies and twin pregnancies achieved after ART born in the Netherlands between 2000 and 2012. *Materials and Methods:* Data were obtained from the Netherlands Perinatal Registry, which covers over 98% of all hospital deliveries. We studied primiparous women from 22 weeks of gestation onwards. We limited our study to opposite sex twin pair deliveries to warrant dizygosity. A total of 6,680 dizygotic twins were included for analyses; 2,407 after IVF/ ICSI pregnancies, 514 after IUI, 472 after OI and 3287 after NC. The perinatal outcomes were gestational age, birth weight, mode of delivery, APGAR score, admission to neonatal intensive care unit, congenital anomalies and perinatal mortality. The maternal outcomes were hypertensive disorders, and maternal postpartum complications. In order to compare differences in characteristics and outcomes between induced and spontaneous conceptions we applied chi-square statistics and Kruskall-Wallis tests. *Results:* We studied 6,680 dizygotic twins, of whom 3,287 conceived natural, 2,407after IVF/ ICSI, 514 after IUI and 472 after OI. The average maternal age at delivery was 32.8 years for IVF/ICSI, 32.3 years for IUI, 29.3 years for OI and 30.0 years after natural conception (p-value $< .001$). Average gestational age at delivery was 35.6 weeks, 35.3 weeks, 35.2 weeks and 35.5 weeks respectively for IVF/ ICSI, IUI, OI and spontaneous conception ($p = .03$). About 50% of the twins were delivered before 37 weeks in all twin groups. The IVF/ICSI and OI twins did not have increased maternal or neonatal risks when compared to naturally conceived twins.The average birth weight was 2,427 gram per child after IVF/ICSI, 2,407 grams after IUI, 2,343 grams after OI and 2,380 grams after NC ($p = .002$). Apgar scores ≤ 7 occurred in 9.53% after IVF/ICSI, 9.86% after IUI and 11.3% after IO and 8.51% after NC (p-value $= .02$), which corresponds to an adjusted odds ratio of 1.19 (95% CI 1.04–1.36) for IVF/ ICSI versus NC, an adjusted odds ratio of 1.25 (95% CI 1.00–1.57) for IUI versus NC, and an adjusted odds ratio of 1.34 for OI versus NC (95% CI 1.07–1.67). Congenital abnormalities occurred in 3.6% IVF/ICSI pregnancies and in 3.81% IUI, 3.61% OI and 3.67% after spontaneous conception (p-value $= .99$). Perinatal mortality (stillbirth plus mortality within 7 days after birth) was respectively 2.01 %, 2.83 %, 2.55 % and 2.07% after IVF/ICSI, IUI, OI and NC (p-value $= .31$). IUI versus natural conception adjusted OR of 1.62 with a 95% CI 1.07–2.46). Hypertension (diastolic pressure $\geq$ 90 mm hg) occurred in 30.0 % of the pregnancies after IVF/ICSI, 36.2% after IUI, 34.5 % after OI and 35.3 % after natural conception. ($p = .0001$).Maternal hemorrhage occurred in 14.8% deliveries after IVF/ ICSI, 13.2% after IUI, 12.1% after OI and in 13.7 % of the deliveries

after natural conception ($p = .29$). *Conclusion:* This study comparing perinatal outcome between induced and natural DZ pregnancies suggests comparable outcomes for twins conceived after IVF/ ICSI, IUI-COH, OI and NC. Differences in perinatal outcome found in singleton pregnancies after IVF cannot be extrapolated to multiple pregnancies.

LOWER PLACENTAL TELOMERE LENGTH MAY BE ATTRIBUTED TO MATERNAL RESIDENTIAL TRAFFIC EXPOSURE: A TWIN STUDY

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Introduction: High variation in telomere length between individuals is already present before birth and is as wide among newborns as in adults. Environmental exposures likely have an impact on this observation, but remain largely unidentified. We hypothesize that placental telomere length in twins is associated with residential traffic exposure, an important environmental source of free radicals that might accelerate aging. Next, we intend to unravel the nature–nurture contribution to placental telomere length by estimating the heritability of placental telomere length. *Materials and Methods:* We measured telomere length in placental tissue of 211 twins in the East Flanders Prospective Twin Survey. Maternal traffic exposure was determined using a geographic information system. Additionally, we estimated the relative importance of genetic and environmental sources of variance. *Results:* In this twin study, variation in telomere length in placental tissue was mainly determined by the common environment. Maternal residential proximity to a major road was inversely associated with placental telomere length: a doubling in the distance to the nearest major road was associated with a 4.92% (95% CI: 1.46 to 8.51%; $p = .006$) longer placental telomere length at birth. In addition, an interquartile increase (22%) in maternal residential surrounding greenness (5 km buffer) was associated with an increase of 3.33% (95% CI: -0.13 to 6.89%; $p = .06$) in placental telomere length. *Conclusion:* In conclusion, we showed that maternal residential proximity to traffic and residential surrounding greenness is associated with shorter placental telomere length at birth. This may explain a significant proportion of air pollution-related adverse health outcomes starting from early life, since shortened telomeres accelerate the progression of many diseases.

STRONG ASSOCIATIONS BETWEEN PARTICULATE AIR POLLUTION AND FETAL GROWTH IN TWINS

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Introduction: Several studies in singletons have shown that maternal exposure to ambient air pollutants is associated with restricted fetal growth. About half of twins have low birth weight compared with 6% in singletons, and twin pregnancies might be more susceptible to external factors. However, to the best of our knowledge, no studies have investigated the association between maternal air pollution exposure and fetal growth in twins. *Materials and Methods:* In 2,222 twins or 1,100 twin pairs (2002–2013) in the East Flanders Twin Register, we studied the association between in utero exposure to air pollution and fetal growth. Births were classified as small for gestational age (SGA) when birth weight was below the 10th percentile of the birth weight for a given gestational age and gender according to cut-off values based on data from twin births in Flanders in the period 2001–2010. Maternal residential addresses at birth were geocoded with a geographic information system. Maternal air pollution exposure was estimated using a spatial temporal interpolation method. Mixed models were used to study fetal growth and maternal residential exposure to PM10, and NO2 over various time windows during pregnancy. *Results:* In 2,222 twins, birth weight averaged (*SD*) 2346 ($\pm$ 2.6). PM10 exposure during pregnancy averaged (25th-75th percentile) 32.0 $\mu g/m^3$(28.7–35.2 $\mu g/m^3$) and 25.9 $\mu g/m^3$(21.0–30.1 $\mu g/m^3$) for NO2. For each 10 $\mu g/m^3$increase in maternal PM10 exposure, birth weight decreased by 53.74 g (95% CI: -105.4 g to -2.1 g; $p = .04$), independent of a newborn's sex, birth order, parity, gestational age (linear and quadratic), birth year (linear and quadratic), season of birth, zygosity and chorionicity, maternal age, median income neighbourhood and insertion of the umbilical cord. The corresponding estimate for NO2 was: -37.75 g (95% CI: -67.7 g to -7.8 g; $p = .01$). After adjustment for a newborn's birth year (linear and quadratic), birth order, parity, season of birth, zygosity and chorionicity, maternal age, median income neighbourhood, cord insertion, the odds ratio for small for gestational age was 1.68 (95% CI: 1.07 to 2.63; $p = .03$) for each 10 $\mu g/m^3$increase in PM10 and 1.29 (95% CI: 0.99 to 1.67; $p = .06$) for each 10 $\mu g/m^3$increase in NO2. *Conclusion:* In twins, a risk group for low birth weight and fetal growth restriction, a significant proportion of fetal growth restriction could be attributed to in utero exposure to particulate air pollution.

INTERGENERATIONAL EFFECT OF PRETERM BIRTH AND SMALL-FOR-GESTATIONAL-AGE AMONG TWINS AND SINGLETONS

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Introduction: Prematurity and small for gestational age are associated with several long-term sequelae. The intergenerational effect of non-optimal birth characteristics, such as preterm birth and small for gestational age, among singletons has previously been investigated. Women born small for gestational age (SGA) have been shown to be more likely to themselves give birth prematurely or give birth to a child born SGA. However, in all studies but one, both twin mothers and twin offspring were excluded from the analyses. Since the etiology of preterm birth is different for twins and singletons it is plausible that the intergenerational effect of non-optimal birth characteristics will be different in these two groups. *Materials and Methods:* A prospective population based register study was performed where all mother-first-born offspring pairs recorded in the Swedish Medical Birth Register were included; in total, 268,867 mothers born in 1973–1983 and their firstborns born in 1986–2009. Information regarding socio-demographic factors such as marital stats and educational level was retrieved from Statistics Sweden, while information with respect to pregnancy and delivery was retrieved from the Swedish Medical Birth Register. Data was stratified according to whether the mothers had been born singleton or twin. Within each strata the relationship between the mother's and the child's birth characteristics were estimated using single and multiple logistic regression. Adjustments were made for maternal grandparent socio-demographics, maternal socio-demographics and birth characteristics (preterm birth and small-for-gestational-age). Birth

outcomes in terms of preterm birth (<37 weeks of gestation) and SGA (<-2SD of the Swedish standard). *Results:* Among mothers born as singletons, being born preterm was associated with an increased risk for delivering a preterm child (OR 1.40, 95% CI 1.29–1.52) while being born SGA increased the likelihood of a SGA child (OR 2.99, 95% CI 2.73–3.26) as well as a preterm child (OR 1.35, 95% CI 1.24–1.46). In twin mothers, the corresponding ORs tended to be lower and the only statistically significant association was between a SGA mother and a SGA child (OR 2.24, 95% CI 1.46–3.42). *Conclusion:* The experience of being born preterm or SGA is to some extent transferred from one generation to the next. Singletons born preterm or SGA have an increased risk for delivering a preterm or SGA infant. Twins have an increased risk for SGA infants only; the risk is lower than for singletons. This knowledge might be of importance when caring for pregnant women who themselves were born SGA or preterm.

WORK–HOME INTERFERENCE AND BURNOUT: A STUDY BASED ON SWEDISH TWINS

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Introduction: Stress-related health problems, such as burnout, are the main reasons for long-term sickness absence in Sweden today, and are increasing in several Nordic countries. This is particularly evident in women. One explanation for women having a higher risk of stress-related ill-health is attributed to women having a more negative work–life balance than men. However, the mechanisms of how work–life balance is related to burnout needs to be further explored. Therefore, the present study sets out to increase the knowledge of how work–home interference (WHI) is related to burnout by taking genetic and early family environmental factors into account. *Materials and Methods:* A total of 4,446 Swedish twins were included in the study. These twins participated in the cross-sectional Study of Twin Adults: Genes and Environment (STAGE) in 2005. Burnout was measured with three items from the Pines Burnout Measure, expressed as the adjectives 'Feeling depressed', 'Being emotionally exhausted' and 'Feeling run down'. The effects of work–home conflict (WHC) and home–work conflict (HWC) on burnout between and within pairs were analyzed with co-twin control analyses comparing between-pair effects and within-pair effects for MZ and DZ twin pairs. *Results:* The results showed that both WHC and HWC were significantly associated with burnout, and that these associations are not affected by age, education, job demands or children living at home. The results from the stratified co-twin analyses showed that familial factors may not be involved in the association between WHC and burnout. However, as regards HWC and burnout, there was a significant difference for between- and within-pair effect for MZ women, suggesting that familial factors may be involved in the association between HWC and burnout. Wald's test showed that the differences for the between- and within-pair effects differed in DZ and MZ twins ($p < .01$), suggesting that genetic rather than shared environmental factors are involved in the associations. *Conclusion:* To conclude, the present study shows that both WHC and HWC are significantly associated with burnout. Women perceive more burnout and slightly more negative interference of work demands on the home domain but not more interference of home demands on work duties. Co-twin analyses point to rather direct associations being present between WHC and burnout but a confounding of genetic factors in HWC and burnout in women. Based on this, by providing knowledge of the mechanisms of WHI and burnout, the present study underscores the utility for employers to improve employees', in particular women's, WHC per se in order to reduce burnout. Moreover, due to genetic confounding in HWC and burnout for women, it is also of significance to take into account women's individual characteristics in order to reduce burnout.

THE MULTIQOL STUDY: A CROSS-SECTIONAL COMMUNITY SURVEY OF QUALITY OF LIFE CONCERNS OF PARENTS OF YOUNG MULTIPLE BIRTH CHILDREN IN AUSTRALIA

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Introduction: The MultiQOL study, conducted in Melbourne, Australia, was the first cross-sectional community survey of quality of life of parents of young multiple birth children, with and without special needs. *Materials and Methods:* Participants ($n = 125$ mothers), whose multiples were aged 18 months to 7 years (mean 5.36 years), were systematically recruited through The Royal Women's and Royal Children's Hospitals, Melbourne. The MultiQOL questionnaire included standardized measures of quality of life and fatigue, the Medical Outcomes Study 12-item Short Form Health Survey (SF-12v2) and a novel instrument (the Multiple-specific Stressors and Uplifts scale) assessing attitudes and experiences specific to multiple parenthood. *Results:* Participants reported significantly poorer quality of life in all domains of the WHOQOL-bréf instrument, compared with age and gender-matched Australian norms ($p < .05$ in the environmental domain, $p < 0.001$ in physical, social relationships and psychological domains). Risk of poor quality of life was elevated 1.5 times in the environmental domain, more than doubled in the physical and social relationships domains, and raised 2.5 times in the psychological domain. Study participants reported significantly poorer wellbeing on both physical and mental component scales ($p < .001$) of the SF-12v2 than age-matched Australian norms. This suggests that problems of compromised maternal wellbeing are not limited to multiples' infancy, but persist. Mothers of multiples with special needs reported even poorer overall quality of life than participants whose multiples did not have special needs ($p < .037$), not explained by mental health problems (which did not differ by children's special needs status). They faced additional psychological and practical challenges, particularly when children were discordant for disability status. Diagnosis of a mental health problem since the multiples' birth was reported by 31% of all participants, most commonly depression with comorbid anxiety. Over 35% of participants reported poor current psychological wellbeing. Fatigue levels were comparable to those of Australian mothers of infants <12 months, regardless of the children's disability status. Analysis of Multiple-specific Stressors and Uplifts responses identified that mothers uniformly acknowledged positive aspects of mothering multiples (uplifts); however, these were not correlated with overall quality of life scores. In contrast, the stressors (the experience of which varied) were consistently associated with diminished overall quality of life scores. The protective influences of partner support, and practical and emotional support from other sources, were demonstrated. Women with access to supportive relationships and practical assistance, who were satisfied with their level of participation in paid employment and with their opportunities for other pursuits apart from child care, enjoyed superior overall

quality of life and reported less psychological distress. *Conclusions:* This study documented the profound and lasting impact of multiple birth for mothers. It demonstrated significant impact on quality of life to mid-childhood, and an association between external supports and maternal quality of life. The challenges experienced by mothers of multiples (including those with special needs) may be governed to a greater extent by extrinsic factors than by individual mothers' psychological vulnerabilities. Results should inform policies for recognition of potential problems, and for provision of services to mitigate them by addressing modifiable factors.

THE LATEST DEVELOPMENT IN TWIN STUDIES

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Introduction: The classical twin study is a powerful heuristic in biomedical, psychiatric and behavioral research and its results have contributed to the awareness that variation in almost every human trait is influenced by genes. In fact, for many phenotypes, heritability estimates derived from twin studies encouraged the search for the responsible genetic variation. Through their collaboration in genome-wide association (GWA) consortia, large twin registries are currently making important contributions to identifying the genetic variation underlying complex traits and disorders. *Materials and Methods:* A review of twin studies in the current era of molecular genetics, including twin studies of, for example, the epigenome, transcriptome, metabolome and microbiome. *Results:* For heritable traits, the comparison of discordant monozygotic (MZ) twins gives valuable information in addition to case-control studies to search for disease-associated biological marks and for the inference of causality. Although MZ twins originate from one zygote, their somatic cells need not always be identical at the DNA sequence level. Copy number variations (CNVs) may differ within MZ pairs and we need to explore, for example, with next generation sequencing (NGS) data and CNVs from microarray studies if such differences contribute to disease risk. *Conclusion:* The classical twin study, combined with novel technologies, represents a powerful approach to identifying and understanding the molecular pathways underlying complex behavioral and other traits.Twin studies need to focus on longitudinal designs, novel technologies, and special groups such as monozygotic twins discordant for (genetic) disorders.

EFFECT OF ASSISTED REPRODUCTIVE CONCEPTION AND ART TYPE ON PERINATAL OUTCOME IN A POPULATION OF 897 TWIN PREGNANCIES

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Introduction: Twin births are at greater risk of adverse perinatal outcome than singletons. However, there is still no consensus about whether the worse outcome associated with twin pregnancies achieved via assisted reproductive tecnique (ART) differ from those caused by twinning itself. *Materials and Methods:* We conducted a retrospective cohort study between January 2003 and December 2013 at the San Pietro FBF Hospital of Rome, a tertiary obstetrical care center. The study aimed to compare obstetrical and neonatal outcome of 376 twin pregnancies conceived with different types of ART procedures (318 FIVET/ICSI; 32 ovulation induction with or without artificial insemination; 24 egg donation) and 521 naturally conceived twin pregnancies. The effect of ART was evaluated using logistic regression for dicothomus outcomes and linear regression for continous ones. The predictor effect on the obstetrical outcome was adjusted for maternal age, parity, pre-existing systemic diseases (diabetes, hypertension, hypothyroidism, thrombophilia), smoke during pregnancy and chorioniocity (783 bicorial biamniotic, 110 monocorial biamniotic and 4 monochorial monoamniotic). Effects on the neonatal outcome were adjusted for maternal age, parity, smoking, gestational age and chorionicity. Adjusted odds ratios with 95%CIs and *p*-values are presented. Post-hoc comparison with Tukey method was used to perform a couple-wise comparison of the ART type effects on the outcome of 370 bicorial biamniotic twin pregnancies achieved via ART. *Results:* Women who conceived via ART were older, more often nulliparous and affected by pre-existing systemic diseases than women who conceived spontaneously. The mean gestational age was significantly lower in the ART group compared to controls (adjusted mean difference -5.33, 95%CI -8.31–2.36***). The incidence rates of gestational diabetes (aOR 2.56 95%CI 1.08–6.49*), abruptio placentae (aOR 2.47 95%CI 1.07–6.29*), antenatal admission (aOR 1.60 95%CI 1.04–2.49*), prophylactic administration of corticosteroid (aOR 1.50 95%CI 1.06–2.15*), severe prematurity (aOR 2.24 95%CI 1.19–4.30*) were higher in women who conceived via ART. Metabolic acidosis was less frequent in ART twins (aOR 0.56 95%CI 0.33–0.95*). No differences in mode of delivery, Apgar score at 5 min, birth weight, congenital anomalies, perinatal mortality, maternal and neonatal length of hospitalization, neonatal intensive care unit admission, and other considered pregnancy and neonatal complications were found between the two groups. Twin pregnancies achieved via egg donation had lower gestational age (adjusted mean difference 1.50 95%CI 1.06–2.15*) and were at greater risk of prophylactic administration of corticosteroid (aOR 3.36 95%CI 1.05–10.8*) and patent ductus arteriosus (aOR 7.71 95%CI 1.33–44.7*) than pregnancies obtained by FIVET/ICSI. Conception by ovulation induction with or without intrauterine insemination was associated with increased risk of maternal thrombocytopenia (aOR 6.42 95%CI 1.16–35.4*) and neonatal neurological complications (aOR 3.42 95%CI 1.10–10.7*) compared to FIVET-ICSI group. *Conclusion:* After controlling for maternal age, smoking, parity, chorionicity and systemic diseases, twin pregnancies conceived via ART are associated with increased obstetrical risk; however, the perinatal outcome is comparable despite a lower gestational age. The type of assisted conception technique appear to have no major detrimental effects on either obstetrical and neonatal outcome.

LOWER GENITAL TRACT INFECTION SCREENING IN TWIN PREGNANCIES FOR PREVENTION OF LATE MISCARRIAGE AND EXTREMELY PRETERM BIRTH.

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Introduction: Twin pregnancies are at increased risk of preterm deliveries and late miscarriage. Several studies on singleton pregnancies suggest that intrauterine infections might account for at least 25–40% of preterm births. A recent Cochrane review concluded that antibiotic treatment with eradication of bacterial vaginosis decreases the rate of late miscarriage. Vaginal smear and treatment of lower genital tract infection were tested in very few studies on twin pregnancies. The aim of this study was to investigate whether screening for lower genital tract infection, followed by antibiotics treatment, decreases the rate of late miscarriage and extremely preterm births in twin pregnancies *Materials and Methods:* Inclusion criteria: all patients referred to our twin clinic between September 2004 and February 2014, <12 weeks of gestational age, managed and delivered at our unit. A multidisciplinary staff made up of obstetricians, psychologists and pediatricians allows the Twin Pregnancy Clinic to provide comprehensive antenatal care. Between 2004 and 2008 no screening for bacterial vaginosis was performed in the first half of

pregnancy. From 2009 a vaginal smear is prescribed during the first trimester. Women with a positive vaginal smear are given specific antibiotic treatment. Exclusion criteria: triplets and first trimester miscarriages. We compared patients who were not screened (n = 295) and patients who were screened for genital infections (n = 198) during the first trimester. Except for introduction of first trimester vaginal smear, our protocol for prenatal care of twin pregnancies has remained the same from 2004 to 2014. The statistical analysis was conducted with the Statistical Package for Social Sciences (SPSS), Windows UK Ltd., Version 14.0. Data of the two groups were compared with the χ^2test (percentage) or Fisher exact test and Student's t test (mean). Differences were considered statistically significant with $p < .05$. *Results:* The two groups were comparable with respect to maternal characteristics except for use of assisted reproductive technologies, which were more frequent in the screened group. The rate of late miscarriage was significantly lower in patients screened for genital infections (2% vs. 6.8%, $p < .05$). Also, extremely preterm birth rate was lower in patients who were screened (1.6% vs. 4%), but the difference is not statistically significant ($p = .21$). The perinatal outcome of patients who were screened and treated was the same as that of patients who screened negative. *Conclusion:* Only a few studies have evaluated the role of screening for genital infections in twin pregnancies; further screening programs were applied only after 24–28 weeks of pregnancy thus considering only preterm delivery. The results of the present study suggest that first trimester screening for genital infections, followed by appropriate treatment of screen positive women, could be useful to decrease late miscarriage in twin pregnancies.

PEDIATRIC BACK PAIN: A TWIN FAMILY CASE CONTROL STUDY INVESTIGATING GENETIC RISK AND ASSOCIATIONS

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Introduction: Low back pain (LBP) contributes substantially to the global burden of disease. Studies assessing LBP have shown that prevalence rates increase with age across adolescence. Longitudinal data have demonstrated that adolescent LBP is an important predictor of LBP in adulthood. Less is known about genetic influence on paediatric LBP. This study primarily aimed to investigate the genetic risk of 3-month life prevalence of LBP and 1-month current prevalence of thoracolumbar back pain (TLBP) in adolescents. Second, the study aimed to identify possible associations between low back pain and other common pain disorders of childhood, restless legs syndrome (RLS), iron deficiency (ID), anxious depression (AD) and multiple sensory sensitivity (MSS). *Materials and Methods:* This study utilised a twin family case-control design with twins aged 11–18 years, their biological parents and siblings. Paper and online questionnaires were sent to 2,479 twin families (across two phases) through the Australian Twin Registry. Parents were asked to complete a validated zygosity questionnaire for their twin children. To assess LBP and TLBP prevalence, all participants were required to indicate areas of pain on a body map, and were asked questions about the duration and frequency of their back pain, and whether or not it was due to injury. Descriptive statistics, χ^2tests and odds ratios (OR) with 95% confidence intervals were used to investigate frequencies and associations across family members and other conditions. The OR for MZ pairs is an upper bound for the risk due to genetic factors. *Results:* There were 653 evaluable responses from twin families (26.3%). Tetrachoric correlation for 3-month life prevalence of LBP was 0.59 and 0.36 for MZ and DZ pairs respectively ($p < .001$). Within twin pairs the OR for LBP was 6.8 ($p < .001$) for MZ, and 3.2 for DZ twins ($p < .005$). For 1 month current TLBP, OR within MZ twins was 7.1 ($p < .001$), but the OR was not significant for within DZ twins (2.2, $p < .160$). A history of prior injury did not influence the analysis for genetic risk of LBP but did have a negative influence on the assessment of genetic risk of TLBP (current). Adjusting for age, LBP in twin individuals was significantly associated with headache (OR 1.91), recurrent abdominal pain (RAP) (OR 2.03), growing pains (GP) (OR 1.79), RLS (OR 1.76) and chronic pain (OR 2.34; all $p < .05$). LBP in mothers, fathers, and first siblings was significantly associated with LBP in twin individuals (all $p < .001$). Additionally, RAP, chronic pain, AD and MSS in mothers was significantly associated with LBP in twin individuals (all $p < .05$). *Conclusion:* Higher MZ ORs for LBP and for TLBP, and significant parental and sibling associations with LBP in twin individuals suggested increased genetic risk on adolescent back pain. Additionally, LBP was associated with several of the common pain disorders and with RLS, consistent with shared genetic vulnerability.

PEDIATRIC ANXIOUS DEPRESSION: GENETIC RISK AND ASSOCIATIONS WITH COMMON PAIN DISORDERS AND RESTLESS LEGS SYNDROME

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Introduction: Anxiety and depression are distinct conditions that share overlapping genetic factors, and are commonly comorbid with different pain conditions. The principal aim of this study was to investigate the genetic risk of pediatric anxious depression (AD) and obtain evidence for association with the common pain disorders of childhood and with restless legs syndrome (RLS). *Materials and Methods:* In Phase 1, questionnaires were sent to 3,909 twin families (twins aged 3 to 18 years, parents and siblings) through the Australian Twin Registry to assess 3-month life prevalence of the common pain disorders and RLS. The questionnaires used for probable diagnostic categorisation of the pain disorders and RLS had been validated or were widely used. In Phase 2, twin families were mailed questionnaires regarding AD (a subscale of the ASEBA Behavioural Checklist). In Phase 3, 1,377 twin families who responded to phases 1 and 2, and 1,102 new twin families were mailed a questionnaire to assess low back pain (LBP) and pain in multiple body regions. Spearman rank correlations were calculated for AD in monozygous (MZ) and dizygous (DZ) twin pairs and casewise concordance determination was used for dichotomous data (clinical AD as defined by ASEBA). Descriptive statistics, χ^2tests and odds ratios (OR) with 95% confidence intervals were used to investigate frequencies and associations. The OR for MZ pairs is an upper bound for the risk due to genetic factors. *Results:* There were 1,017 evaluable responses from twin families (26.02%). Spearman's rank correlation for AD was 0.84 and 0.71 for MZ and DZ pairs respectively ($p < .001$). When binary analysis was used, clinical AD was recorded for 107 twin individuals (5.3%), and casewise concordance was 0.47 for MZ and 0.19 for DZ twin pairs. Adjusting for age, AD as a continuous variable (0–26) in twin individuals was associated with RLS (OR 1.06), migraine (OR 1.11), recurrent abdominal pain (RAP; OR 1.09) and chronic pain (CP) (OR 1.09) (all $p < .01$). The perception

of relatively low odds ratios is reflective of AD being analysed as a continuous variable (0–26) rather than dichotomous. AD in mothers, fathers and oldest siblings was significantly associated with AD in twin individuals (all $p < .001$). Additionally, AD in mothers was associated with migraine (OR 1.06, $p < .001$) and LBP (OR 1.05, $p = .02$) in twin individuals. *Conclusion:* Childhood AD was associated with several of the common pain disorders and with RLS. MZ twin concordances, and parental and sibling associations with twin individuals support an interpretation of increased genetic risk of AD. The extent to which the association between AD and the pain disorders and RLS is causal, consequential or involves pleiotropy will be addressed.

MIRROR SYNDROME AFTER FETOSCOPIC LASER THERAPY FOR TWIN-TWIN TRANSFUSION SYNDROME - A CASE REPORT

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Introduction: The mirror syndrome, also called triple edema or Ballantyne syndrome, is a rare condition where there is an association of maternal edema, fetal hydrops and placental edema. The pathogenesis of this syndrome is unknown. Different situations (multiple pregnancy, isoimnunization Rh, infections) have reportedly been present with this syndrome. A poor obstetric outcome is the rule. *Materials and Methods:* Case report. *Results:* We report a case of a 38-year-old woman with a monochorionic diamniotic pregnancy, complicated at 23rd week of gestation by a twin-twin transfusion syndrome (TTTS), with the recipient fetus presenting hydrops and cardiomegaly (TTTS in stage IV). A fetoscopic laser therapy was successfully performed. One day after this procedure, the mother presented an intensive edema, oliguria, and hemodilution, without signs of hypertension or proteinuria. She was controlled with diuretic therapy and stayed in a weekly control (clinical and ultrasound). Although the ex-recipient fetus had a persistent cardiomegaly, the ventricular function improved. At 34th week, two live infants were delivered by cesarean C-section. *Conclusion:* Mirror syndrome manifested after fetoscopic laser therapy in TTTS, with a receiver hydrops, does not necessarily predict a poor obstetric outcome.

EARLY RESPIRATORY INFECTIONS: GENETIC FACTORS, FAMILY ENVIRONMENT AND PASSIVE SMOKING

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Introduction: Early respiratory infections are important risk factors for respiratory disease in adulthood. Objectives of this study were: (1) to estimate the genetic and environmental components of early respiratory infections; (2) to test the hypothesis that passive smoking exposure modifies the relative weight of environmental and genetic factors on susceptibility to these infections. *Materials and Methods:* Study subjects were about 1,000 twin pairs aged 3–17 years and enrolled in the Italian Twin Registry (ITR), a nationwide database comprising pairs of twins who accept to participate in medical and scientific research activities. Study outcomes were respiratory infections before the first 2 years of life — for example, bronchitis, wheezy bronchitis, pneumonia and bronchiolitis — as reported by parents in a general health questionnaire. Questions on these infections follow the Italian enriched version of the ISAAC questionnaire, which investigates respiratory diseases with a focus on environmental risk factors and family history. The statistical analysis was based on the twin method that compares measures of concordance in monozygotic and dizygotic twins. For each respiratory infection the proportion of variance explained by genetic factors, by environmental factors shared by the twins and by individual environmental factors were estimated. Furthermore, the same analysis was performed stratifying by passive smoking defined as at least one of the parents smoking in the house and/or in the car. *Results:* No genetic influence was found on bronchiolitis (prevalence 11%), for which 95% of the total variation was explained by environmental factors shared by the twins; this result did not change when stratifying by passive smoking. For bronchitis (prevalence 40%), genetic factors explained 16% of total variation and again a strong influence of shared environmental factors (83%) was detected; no difference was seen in the stratified analysis. For wheezy bronchitis (prevalence 11%) and pneumonia (prevalence 7%), a considerable contribution of both genetic and environmental factors emerged. Furthermore, the relative importance of these factors changed when stratifying for parental smoking. In detail, the shared environmental component increased for smokers' children while the genetic component became more important in the non-smokers' group. *Conclusion:* The study found a substantial effect of shared familial environment in the development of early respiratory infections. For pneumonia and wheezy bronchitis, parental smoking was suggested to account for a relevant proportion of the shared environmental component. Furthermore, susceptibility genes for these infections may be more easily detectable in children not exposed to passive smoking.

PROGNOSIS FOR AN ISOLATED SINGLE UMBILICAL ARTERY IN TWIN PREGNANCIES

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Introduction: Isolated single umbilical artery in singleton pregnancies may be associated with growth restriction (IUGR) and adverse pregnancy outcome and this has also been reported in twins in a small number of studies. We aimed to compare cases of isolated SUA in twin pregnancies with individually paired, consecutive, normal twin pregnancies. *Materials and Methods:* We examined all cases of SUA in twins diagnosed by second trimester ultrasound at our tertiary referral centre (Melbourne, Australia) over 7.5 years. Diagnosis was confirmed by placental histopathology or by expert review of ultrasound images. Color Doppler was used to visualize the umbilical arteries, both adjacent to the fetal bladder and in a section of a free loop of cord. Co-existent aneuploidy or major anomalies were excluded. Each case of isolated SUA was assigned three consecutive controls paired for chorionicity and maternal age. Primary outcomes were preterm birth <34 weeks, small-for-gestational-age (SGA) or perinatal death. Other outcomes included antenatal IUGR, mode of delivery, and admission to neonatal intensive care or special care nursery. *Results:* Nine pregnancies (18 fetuses) were identified for analysis as cases out of 1,243 twin pregnancies in the same period (0.72%). There were no background differences between cases and controls. All twins were discordant for SUA. Isolated SUA was associated with preterm birth <34 weeks (odds ratio 12.2, 95% confidence interval 2.0–75.2, $p = .005$) but there was no difference in the mode of delivery. There were no differences in SGA or antenatal growth restriction between cases and controls, and there were no

differences between the affected twin and its normal co-twin. Perinatal death was increased, but after controlling for gestational age and clustering this finding was no longer significant. *Conclusion:* The literature on isolated SUA in twin pregnancies is scarce with concerns generally focusing on preterm birth, intrauterine growth restriction or SGA. Our series confirms an increased risk of preterm delivery at <34 weeks; however, there was no increase in antenatal intrauterine growth restriction nor of postnatal SGA. Indeed, within the cases, the infant with the SUA was slightly larger at birth than the other twin. On reviewing the cases, most preterm deliveries were spontaneous in onset and not iatrogenic. Twin pregnancies are inherently high-risk pregnancies and require regular surveillance for growth restriction, but our findings suggest that the finding of an isolated SUA may not increase this requirement. The increased risk of preterm delivery may have clinical implications for timely admission and corticosteroid administration in individual circumstances.

EARLY PRENATAL DIAGNOSIS OF CHORIONICITY AND AMNIONICITY IN TWIN PREGNANCY BETWEEN OPERATORS WITH DIFFERENT DEGREES OF EXPERIENCE: THE ROLE OF LEARNING METHOD.

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Introduction: Twin pregnancy has a disproportionate effect on perinatal mortality; monochorionic twins (MC) have an approximately 3-to 5-fold increased perinatal morbidity compared to dichorionic twins (DC). For these reasons attempts have been made to correctly assign chorionicity ultrasonographically using single or composite parameters. The aim of this study was to demostrate the importance of learning method to evaluate the correct diagnosis of chorionicity and amnionicity in the first trimester allowing a correct management of these high risk pregnancies. *Materials and Methods:* The study lasted 5 years (January 2008–December 2012) and was conducted at an Italian referral center for fetal pathologies; it involved the patients who attended our Unit for first trimester genetic screening at 11 + 6 and 13 + 6 weeks. Twenty-four trainees with different degrees of experience in fetal medicine were asked to examine the chorionicity and amnionicity in twin pregnancies at 11 + 6 and 13 + 6 weeks. We classified as proficients the trainees with more than 3 years of experience in fetal medicine, as intermediate those with more than 1 year but less than 3 years, and inexperienced those with only 1 year. Each scan was performed in the presence of a highly trained sonographer. For every US analysis images and/or video clips were recorded and stored; at the end of working day the data about every US examination were analyzed and discussed. The study period took place over 6 months and was divided in two different steps: the first (1st–3rd months) in which the trainees performed the diagnosis of chorionicity and amnionicity according to their own knowledge about twin pregnancies. The second step (4th–6th months), the subsequent comparison with the diagnosis was made by supervising doctor and the analysis of images and video clips in which the diagnoses by trainees was carried out according to their new knowledge about twins. The percentage of unsuccessful diagnoses was calculated for each trainee in both periods. *Results:* A total of 200 twin pregnancies were analyzed. Each trainee carried out 25 examinations. Four trainees were experienced, 14 intermediate and 6 inexperienced.The failure rate was different according to the study step and the operator's experience; in the first step 4 out of 6 (66%) of inexperienced trainees, and 6 out of 14 intermediate trainees (42%) met difficulties in recognizing the right number of gestational sacs; 4 out of 6 inexperienced and 6 out of 14 intermediate trainees failed in the case of the 'black lambda sign'. None of the inexperienced and intermediate trainees tried to look for umbilical cord insertions in case of uncertain chorionicity. Five out of six inexperienced (83%) and ten out of fourteen intermediate (71%) trainees did not try to recognize if the fetuses were fused (conjoined twins) in the case of monoamniotic pregnancy.None of the inexperienced and 10 out of 14 trainees (71%) did not attemp to count the number of yolk sac in case of uncertain amnionicity. In all cases, the proficient trainees carried out the right diagnosis. In the second step, the failure rate was considerably lower; among inexperienced trainees two out of six (33%) failed to recognize the number of gestational sacs, which was the same for three of fourteen intermediate trainees (21%). All the trainees investigated umbilical cord insertions in cases of uncertain chorionicity and the number of yolk sacs when the amnionicity was not clear. All the trainees paid attention to identifying eventual fused fetal bodies of twins in case of monoamniotic pregnancy. The average time per case required to conclude the diagnosis of chorionicity was different according to the study step and operator's experience. In the first step: 4 min (2–7 min) for proficients, 6 min (4–8 min) for intermediate and 7.5 min (5–10) for inexperienced trainees; fewer for amnionicity. In the later step the average time per case was unchanged for proficients, 5 min (3–7 min) for intermediate and 6 min (4–8 min) for unexperienced trainees. *Conclusion:* Competency in twin pregnancies is paramount and is required to achieve the right diagnosis of chorionicity and amnionicity for appropriate counseling, decision-making and management. The median number of scans required to achieve the right diagnosis of amnionicity and chorionicity may be 17 (range 10–25) for inexperienced trainees, and 15 (range 10–20) for intermediate trainees.

CHARACTERIZING DNA METHYLATION HERITABILITY ACROSS THE GENOME

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Introduction: The biological mechanisms that drive DNA methylation are mostly unknown, but there is evidence that genetic factors are involved. The classical twin model allows the estimations of these effects by comparing DNA methylation similarity between MZ and DZ twin pairs. *Materials and Methods:* In this study we used Infinium HumanMethylation450 BeadChip data from whole blood samples of 94 MZ and 25 DZ female twin pairs to estimate the heritability of methylation sites across the genome. The observed methylation variance was partitioned into additive genetic, shared environmental, and unique environmental factors using the ACE model. *Results:* The genome-wide mean heritability across 349237 autosomal CpG-sites was estimated at 18%. Similar results were obtained in previous estimates from adipose tissue. Altogether, 57382 out of 349237 CpG-sites (16%) had evidence for strong heritability ($h2 > 40\%$). The classification of methylation sites by genomic region revealed that intergenic regions had higher heritability values, while sites located in the first exon or within 200bp of the TSS had the lowest estimates of heritability. A similar classification by location in relation to CpG islands revealed that sites in CpG island shores had the greatest heritability estimates, while those in CpG islands were least heritable. Genetic effects at heritable CpG sites were further confirmed by estimating methylation quantitative loci (meQTL) in 94 MZ twins using HapMap II imputed genotypes.

Overall, 14% of heritable (h2 > 40%) CpG-sites were observed to harbour a meQTL. *Conclusion:* We observed evidence for heritability of DNA methylation at 16% of CpG-sites genome-wide. The strongest genetic effects on DNA methylation were observed at CpG-sites in intergenic regions and outside of the CpG islands. Further analyses may reveal novel regulatory functions of the regions under genetic control and assess their relative importance in different tissues.

PEDIATRIC RESTLESS LEGS SYNDROME WITH OR WITHOUT GROWING PAINS: NOVEL INSIGHTS FROM A TWIN FAMILY STUDY.

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Introduction: Pediatric restless legs syndrome (RLS) and growing pains (GP) have clinical similarities. We published evidence from a previous twin family study that their strong association might have a genetic basis. We have now conducted a novel twin family case-control study, considering three outcomes based on RLS with and without GP. *Materials and Methods:* Questionnaires were mailed to 3,909 twin families (twins aged 3 to 18 years, parents and siblings) through the Australian Twin Registry to assess 3-month lifetime prevalence of the common pain disorders of childhood and associated conditions (RLS, parent-reported doctor confirmed iron deficiency [ID], anxious depression [AD, by ASEBA Behavioural Checklist] and multiple sensory sensitivity [SS]). The RLS criteria were those of Allen et al. (2003) with exclusion where feasible of alternative diagnoses. GP criteria were derived from Peterson (1986). Familial and other associations were estimated as odds ratios (ORs) to allow comparisons. The OR for MZ pairs is an upper bound for the risk due to genetic factors. *Results:* There were 1,017 evaluable responses from twin families (26.1%). Results were analyzed according to whether participants met criteria for three mutually exclusive and independent traits: having GP (only), having RLS (only), and having both RLS and GP. For having RLS (only), there was evidence consistent with a genetic etiology; the OR within MZ pairs was 10.5 ($p < .001$), and 8.1 for DZ pairs ($p < .001$). Recurrent abdominal pain (RAP), chronic pain, ID, AD and SS were associated with having RLS (only) (all $p < .01$), the strongest association being with ID (OR 5.8, $p < .001$). For having RLS and GP, the ORs within MZ twin pairs was 38.9 ($p < .001$) and 6.5 for DZ twins ($p < .001$). Low back pain (LBP), RAP, headache and ID (OR 2.1, $p = .04$) were associated with RLS and GP (all $p < .05$). For having GP (only), the OR within MZ twin pairs was 13.7 ($p < .001$) and 6.0 for DZ pairs ($p < .001$). Headache was the only condition associated with having GP (only) (OR 2.06, $p < .001$). GP was not associated with ID (OR 1.2, $p = .5$). Within all three conditions, a family member (mother, father, first sibling, and co-twin) having the outcome of interest (RLS (only), RLS and GP, and GP (only) was significantly associated with the respective condition in twin individuals (all $p < .001$). *Conclusion:* For RLS (only), genetic factors were associated with at most a small increase in risk, and there was a stronger association with ID which is known to have causal implications. For the combined phenotype RLS and GP, genetic factors might be associated with substantial increase in risk and there was only a weak association with ID. For GP (only), genetic factors were associated with at most a modest increase in risk, and there were no associations with pain disorders, ID or AD. Our data were consistent with these three independent traits having different aetiological influences, and further insights into both RLS and GP might come from investigating them as such.

PARENT-REPORTED IRON DEFICIENCY: GENETIC RISK AND ASSOCIATIONS WITH THE COMMON PAIN DISORDERS OF CHILDHOOD

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Introduction: Several genome-wide association studies have identified genes associated with human iron parameters, including stores. Iron deficiency (ID), however, has not previously been shown to be genetically determined except for rare genetic variants. Iron deficiency is associated with fibromyalgia in which there is sensitivity to pain, and has been shown experimentally to be associated with increased sensitivity to pain. There is evidence that iron deficiency is causally associated with restless legs syndrome (RLS) which we have found in turn to be associated with common recurrent pain disorders of childhood. This twin family study was conducted to explore the genetic risk of pediatric ID, to extend known relationships with RLS, and to identify possible associations with the common pain disorders of childhood. *Materials and Methods:* Questionnaires were sent to 3,909 twin families (twins aged 3 to 18 years, parents and siblings) through the Australian Twin Registry to assess 3-month lifetime prevalence of the common pain disorders of childhood including growing pains (GP), migraine, headache, recurrent abdominal pain (RAP), low back pain (LBP) and chronic pain (CP), as well ID and RLS. Validated scales where applicable were used for probable diagnostic categorisation of these pain disorders and RLS. For ID, lifetime prevalence was assessed by parental-report, and cases where doctor diagnosis was not confirmed were omitted. Descriptive statistics, chi-square ($\chi 2$) tests and odds ratios (OR) with 95% confidence intervals were applied to examine frequencies and associations. The OR for MZ pairs is an upper bound for the risk due to genetic factors. *Results:* There were 1,017 evaluable responses in which 87 twin families (8.6%) had at least one twin with a history of ID. Tetrachroric correlation for ID was 0.85 and 0.68 for MZ and DZ pairs respectively ($p < .001$). The within twin pairs ORs were 48.8 ($p < .001$) for MZ, and 15.8 ($p < .001$) for DZ twins. Twin individuals with ID had significant age-adjusted associations with RLS (OR 4.03), migraine (OR 2.20), RAP (OR 2.30), and chronic pain (OR 4.51) (all $p < .05$). ID in mothers (34.7%) significantly increased the risk of twin individuals having ID, (OR 2.4), RLS (1.72), RAP (1.74) and CP (1.70) (all $p < .05$). Paternal ID was infrequent, and had no significant associations with conditions in twins (OR 2.27, $p = .15$) however ID in first siblings was significantly associated with ID in twin individuals (OR 5.43, $p < .001$). *Conclusion:* The MZ/DZ within pairs ORs and the associations between ID in family members and twin individuals were consistent with increased genetic risk on parent reported life prevalence of pediatric ID. These results are congruent with previously reported genetic influence on iron parameters. Childhood and maternal ID were associated not only with RLS as expected, but also with several of the pain disorders. We have proposed a model illustrating potential causal influence of ID (including dopaminergic mechanisms) on the vulnerability to these pain disorders.

NOVEL ATHERO-PROTECTIVE BIOMARKER ANTI-OXCL – HERITABILITY AND GENETIC CO-REGULATION WITH ANTI-PC AND TRADITIONAL CVD BIOMARKERS

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Introduction: AntiOxCL and antiPC, antibodies against oxidized cardiolipin and phosphorylcholine, respectively, have recently proven to be negatively associated with the risk of cardiovascular disease (CVD) and thus may carry information about athero-protection in CVD development. The blood concentration of antiOxCL varies substantially among individuals and is approximately normally distributed, pointing towards a complex regulation influenced by many factors. However, the relative importance of genetic and environmental effects on circulating antiOxCL levels is unknown. Here, we provide the first estimate of the heritability of antiOxCL in a large twin material. We also systematically investigated the correlations between antiOxCL and traditional CVD biomarkers as well as with antiPC, and subsequently estimated potential shared genetic and environmental effects by covariance partitioning. *Materials and Methods:* Serum levels of antiOxCL, antiPC and 9 more traditional CVD biomarkers (Lp-PLA2, CRP, TC, TG, HDL, LDL, ApoA1, ApoB, HbA1c) were measured in elderly Swedish twins born between 1911 and 1958 ($N = 1958$). All variables were adjusted for age and sex by linear regression and residuals were rank order normalized. Intra-individual (phenotypic), intra-pair and cross-twin cross-trait correlations were calculated. Heritability, bivariate heritability and genetic correlations were estimated by univariate/bivariate variance component maximum likelihood methods implemented in structural equation modeling using the OpenMx package in R. *Results:* 39% of the variance in antiOxCL levels could be attributed to additive genetic variation. There was no significant evidence for dominant genetic and common (shared) environmental components. AntiOxCL was moderately and significantly correlated with antiPC (rpheno = 0.31) and weakly but still significantly correlated with TC, HDL, LDL, ApoA1 and ApoB. AntiOxCL was not significantly correlated to Lp-PLA2, CRP, TG and HbA1C. For all biomarkers that showed significant correlations with antiOxCL, the bivariate heritability was greater than 50%, while the genetic correlation with antiOxCL was markedly more pronounced for antiPC (rG = 0.54) than for the other biomarkers. *Conclusion:* Human serum antiOxCL levels are partly influenced by additive genetic effects. AntiOxCL was more related to antiPC than to other more traditional CVD biomarkers such as blood cholesterols and apolipoproteins (TC, ApoA1 and ApoB), that showed weaker but still significant correlations. The correlation between antiOxCL and antiPC was mostly due to shared genetics.

CAUSES OF VARIABILITY AND CORRELATIONS AMONG BIOMARKERS OF CARDIOVASCULAR DISEASE - TWIN VERSUS GENOME-WIDE COMMON SNPS MODELS

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Introduction: Heritability estimation is a crucial step to understand the relative importance of genetic and environmental effects on phenotypic variation of human diseases and complex traits. Pedigree approaches of estimating heritability are based on modeling the similarity among relatives. The classical twin model offers a way to handle confounding influences from shared environmental effects but is based on strong assumptions. Here we compare the variance components, genetic covariance and correlation underlying the framework of cardiovascular disease (CVD) related biomarkers explained by genome-wide common SNPs using a method called Genome-wide Complex Trait Analysis (GCTA) that has emerged in recent years. *Materials and Methods:* Serum levels of 10 CVD related biomarkers (total cholesterol, triglycerides, HDL, LDL, ApoA1, ApoB, CRP, HbA1C, Cystatin C, Creatinine) were measured in up to 12,591 Swedish twin individuals born between 1911 and 1958. Genotypes of one MZ twin and both DZ twins ($N = 9{,}896$, 644,556 SNPs after QC) were available for a majority of the subjects. All serum levels were adjusted for age, sex (and zygosity for GCTA) by linear regression and residuals were rank order normalized. Phenotypic and within twin-pair correlations were calculated. Univariate and bivariate heritability and genetic correlations were estimated by twin-based structural equation modeling (SEM) and GCTA. *Results:* In the framework of the 10 CVD biomarkers, tagging by common SNPs (MAF > 0.01) could explain 34∼97% of the narrow-sense heritability (h2SNP = 0.135∼0.318) as estimated from twin-based SEM. The bivariate heritability was weak among all pairs of biomarkers, but the genetic correlation (as estimated by GCTA) was generally more pronounced and more than 0.6 between TC-LDL, TC-ApoB, HDL-ApoA1, LDL-ApoB and Cystatin C-Creatinine. *Conclusion:* Genome-wide common SNPs partly explain the phenotypic variance of CVD biomarkers, and robustly capture genetic correlations between several members of the CVD biomarker network, in particular, total cholesterol-LDL, total cholesterol-ApoB, HDL-ApoA1, LDL-ApoB, and Cystatin C-Creatinine.

SELECTIVE REDUCTION USING INTRAVASCULAR POTASSIUM CHLORIDE INJECTION AFTER LASER SURGERY FOR TWIN-TWIN TRANSFUSION SYNDROME

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Introduction: Selective reduction (SR) via intravascular potassium chloride (KCl) injection is contraindicated in monochorionic diamniotic twins due to placental vascular communications that can serve as a conduit for passage of the KCl to the co-twin. After successful selective laser photocoagulation of communicating vessels (SLPCV) for twin-twin transfusion syndrome (TTTS), the circulatory systems of the twins are rendered independent of one another, thereby creating a 'functional dichorionic' twin gestation. We set out to describe our experience with SR using intravascular KCl injection after SLPCV. *Materials and Methods:* TTTS patients treated with SLPCV by members of the USFetus Consortium between 2003 and 2013 that underwent subsequent SR were retrospectively studied. SRs were performed at non-USFetus centers. Data regarding perinatal outcomes were acquired from a prospectively collected database. *Results:* Of 1069 TTTS patients that underwent SLPCV, three (0.3%) underwent subsequent SR. The SR patients underwent SLPCV at 18 0/7, 22 6/7, and 23 0/7 weeks gestational age (GA) for Quintero Stage III, IV, and III TTTS, respectively. SR was performed at maternal request due to uncertain neurological outcome; the GA at SR and indication for SR were: (1) 22 6/7, donor with prominent lateral ventricles and hypoplastic cerebellar vermis, (2) 24 4/7, recipient with ventriculomegaly (1.2 cm), (3) 23 6/7, donor with ventriculomegaly (1.4 cm). The time from SLPCV to SR was 34, 12, and 6 days, and latency from SR to delivery was 72, 43, and 84 days. GA at delivery was 33 1/7, 30 5/7, and 35 6/7 weeks'

gestation. All co-twins survived post SR, and no short-term neurological sequelae were suspected after birth.

Conclusion: Selective fetal reduction may be considered, with careful counseling, after successful laser surgery for TTTS. Further study, including formal neurodevelopmental testing of the co-twins, should be conducted before SR can be routinely considered after SLPCV.

POSTNATAL DEPRESSION SYMPTOMATOLOGY AND BREASTFEEDING

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Introduction: Postnatal depression affects approximately 13% of women within the first 3 months postpartum. Previous studies have found that women who have postnatal depression breastfeed for less time. However, the direction of causation is unclear. Are women with depression less likely to breastfeed or are women who breastfeed less likely to become depressed? Is the relationship bidirectional, or does a third variable account for this association? Both breastfeeding and postnatal depression are heritable (h2 = 54% and h2 = 38%, respectively). Our aim was to test whether the association between breastfeeding and depressive symptomatology in the postpartum could be explained by an overlap in latent genetic or environmental factors that influence them. *Materials and Methods:* Participants were 3,364 female twin mothers of the Australian Twin Registry born between 1892 and 1971, who were surveyed by a mailed questionnaire including information about their childbearing and in some cases, by an interview over the telephone, in 1988–1993. There were 992 complete twin pairs, 629 monozygotic and 363 dizygotic, and 1380 individual twins from incomplete pairs. Data were based on retrospective self-reports. Both *z* cores of breastfeeding mean duration (BF) to all the children and the mean number of reported episodes of postnatal depression symptoms (EPDS) were the variables for our analyses. We conducted a bivariate model in which the A, C and E matrix are specified in a Cholesky decomposition. BF was used as the first and EPDS as the second latent factors. Age at the survey time was used as covariate. Statistical analyses employed full information maximum-likelihood modelling procedures using the statistical package Mx. *Results:* The mean number of children was 2.52 (*SD* = 1.26). The mean duration of breastfeeding was 5.31 months (*SD* = 4.69). A total of 1,143 women (34%) reported feelings of depression after at least one birth. The mean number of episodes of postnatal depression symptoms was .53 (*SD* = .90). The correlation between BF and EPDS was rph = 0.09 (95% CI: 0.05, 0.12). A bivariate AE model provided the best fit of the data. The genetic factor ABF, loading primarily on BF and accounting for 54% of its variance, also accounted for 3% of EPDS variance. The specific genetic contribution to EPDS was 22%. The unshared environmental factor (EBF) accounted for 46% of BF variance, but did not account for any variance in EPDS. While neither the genetic correlation between BF and EPDS (ra = .11, 95% CI: -.04, .25) nor the environmental one (re = .04, 95% CI: -.03, .12), were significant, there was a significant relationship between the two traits and the A and E cross paths between BF and EPDS could not be dropped simultaneously. *Conclusion:* Our study confirmed that women that report symptoms of postnatal depression breastfeed for less time, although this association was of a limited magnitude. We had insufficient power to detect the origin of this association. However, based on the point estimates, the relationship appears to be due to shared genes. Further research is needed to understand the nature and causes of the association between breastfeeding and postnatal depression.

WHY BIOMARKERS IN TWIN RESEARCH?

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Introduction: Increasing development of new technologies has enhanced the potential for using biomarkers in population research. The advantages of using twins includes the full or partial matching on genome and early life exposures starting from conception, ease of obtaining specimens, and conducting long term follow-up. *Materials and Methods:* Potential study designs unique to twin registries include: (1) Comparison of MZ and DZ pairs to assess the contribution of genetics and shared environment to variation in a biomarker (i.e., heritability); (2) Comparison of biomarker levels within exposure-discordant pairs to examine the effect of environmental exposures on biomarkers with minimized confounding by unmeasured genotype and shared early environment; (3) Examination of gene-environment interaction at the individual or pair level; (4) Use of unaffected MZ twins of cases as pre-disease surrogates for comparison with other controls when cases either are not available or when disease alters the biomarker itself; (5) Screening and follow-up of the unaffected twins of cases as a high risk cohort (especially when biomarkers of precursor conditions are available); (6) Comparison of biomarkers within members of disease-concordant twin pairs by age at onset; (7) Comparison of biomarkers in disease-concordant twin pairs to non-twin familial cases; and (8) Designing interventions using biomarkers to alter an adverse phenotype in one twin. *Results:* Several examples of each of these study designs will be presented. *Conclusion:* Twins offer unique opportunities for using biomarkers to understand disease etiology and predict risk.

RISK OF LYMPHOMA ATTRIBUTABLE TO THE GENOME: A TWIN STUDY

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Introduction: We previously reported a high attributable risk of Hodgkin lymphoma (HL) in the monozygotic co-twins of young adult cases, and a lesser modest elevation in the co-twins of non-Hodgkin lymphoma (NHL) cases (Mack et al., NEJM 1995). After 18 additional years of follow-up, we now update the empirical estimates of risk of hematological malignancy (HL, NHL, chronic lymphocytic leukemia-CLL and multiple myeloma-MM) to the co-twins of cases. *Materials and Methods:* Proband cases volunteered in response to advertising in periodicals across North America, zygosity was established by standard questions, and co-twins were initially identified and described. For this report, each healthy co-twin was traced and information collected directly or by means of information collected through the National Death Index. Person-years after the proband diagnosis were enumerated according to calendar year, age, gender, race, pre- or post-ascertainment, and date of last contact. Applying information from the National Surveillance, Epidemiology, and End Results (SEER) program to the person-years of follow-up by calendar year and age for each lymphoma category, the expected number of cases was calculated. By comparing the observed number of neoplasm-specific diagnoses to the expected number, a standard incidence ratio was calculated separately for the co-twins of dizygotic (DZ) and monozygotic (MZ) twin cases. The microscopic pathology of each case was separately confirmed by a hematological pathologist (BNN). *Results:* The strong genetic attribution of risk initially found for (young adult) HL was confirmed, with risk to the unaffected co-twin of a case 13.5 times that

expected. Our initial failure to identify a genetically determination for NHL was repeated after long follow-up, with the observed number of observed DZ and MZ cases both in excess, suggesting stronger environmental determination. As expected, based on the known family clustering, the number of observed CLL cases also exceeded the number expected, and the single observed MZ co-twin case of MM was also excessive, albeit consistent with chance. *Conclusion:* Interpretation: The strong genetic determination of (young adult) HL was confirmed. No evidence for the genetic determination of NHL was found, but the ICD-9 codes available did not permit accurate subclassification. A suggestive excess of CLL in MZ co-twins confirmed expectations, and the single case of MM in a co-twin of a case of MM provides a suggestive anecdote.

TWIN STUDIES ELUCIDATE ETIOLOGY OF ADOLESCENT/YOUNG ADULT HODGKIN LYMPHOMA

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Introduction: There is evidence strongly suggesting that both early childhood environment and heritable risk factors are important in the etiology of adolescent/young adult Hodgkin lymphoma (AYAHL). We designed a series of twin studies with AYAHL patients, their twins and spouses identified from the International Twin Study, to further clarify the nature of the environmental and genetic risk factors. *Materials and Methods:* We received completed and mailed questionnaires from 188 twin pairs (out of 250 total pairs, 75% response rate), and compared responses in a matched case-control study. Cytokine levels were measured by ELISA in supernantants collected from blood samples 90 unaffected MZ twins of AYAHL cases and non-blood relatives as controls. (Unaffected twins of cases were used pre-disease surrogates because the disease effects cytokines). Fecal microbial diversity was evaluated in a small number of AYAHL-discordant pairs using 16S rRNA sequencing and a bioinformatics pipeline. DNA samples from 133 concordant and discordant twin AYAHL patients were pooled with samples collected from our population-based studies and genotyped using the Illumina 660Quad Bead Array, and ultimately combined in a meta-analysis with a large European GWAS. Conditional and unconditional logistic regression, ANCOVA and *t* tests were used for statistical analysis. *Results:* The twin who reported more early childhood fecal-oral exposures had an 80% decreased risk of AYAHL (Odds Ratio = 0.2, 95% confidence interval = 0.1, 0.6). Consistent with these results, the unaffected twin of the pair had significantly higher gut microbial diversity in fecal samples compared to their affected case twin (p = .015). Immunologically, risk was associated with higher levels of an inflammtory, B-lymphocyte activating Th2 cytokine (interleukin-6) and lower levels of a Th1 cytokine (IL12) (p = .002) important for controlling viral infections, in the comparison between unaffected MZ twins of cases and controls. In the GWAS studies, we found independent genome-wide significant associations between AYAHL risk and loci in HLA class I and class II genes, as well those located in IL13 (a Th2 cytokine) and TCF3 genes. As expected, the mean risk allele score was significantly higher among cases with affected non-twin family members compared to sporadic cases (p = .008). However, AYAHL-concordant twins had a lower mean risk allele score compared to sporadic cases, perhaps suggesting a stronger role of environment or rare mutations. We also found that AYAHL case-twins had significantly higher DNA methylation levels at the TCF3 GWAS locus (which happened to be located in a CpG island) compared to their unaffected twins (9 AYAHL discordant pairs, p = .05). There was no difference in DNA methylation at the same locus between members 25 healthy twin pairs (p = .81). *Conclusion:* Based on our twin studies, the risk factors for AYAHL fit a hygiene hypothesis model with additional risk contributed by genetic variants affecting other aspects of the immune response. Unaffected MZ twins of patients may be used as pre-disease surrogates to study heritable biomarkers when the biomarker is affected by disease. Comparisons of risk allele scores among disease-concordant twins to other types of cases can provide information on common versus rare variants and help direct selection of subjects for further study.

BIOSPECIMENS FOR TWIN RESEARCH: WHAT AND HOW?

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Introduction: Biospecimens add power to twin studies by providing a biological link to phenotype and provide an opportunity to investigate the main components of phenotypic variation. However, there is often confusion about the most appropriate specimens to collect for such studies. *Materials and Methods:* This talk will detail the main biospecimens that can be collected from twins, from birth to old age, such as placenta, cords, blood, saliva and tumor samples. It will provide guidelines for collection, transport and storage to maximize their utility. This talk will also discuss the myriad ways to which biospecimens can be used for downstream 'omics' applications, from genomics, to epigenomics, metabolomics and beyond. *Results:* Such downstream applications can be performed on a multitude of samples. Although specimens stored in a variety of conditions can be used for multiple platforms, each platform comes with its own set of ideal collection and storage conditions. The talk will be valuable to all those wishing to maximize on the utility of their stored samples as well as those planning to collect biosamples. It will also focus on specific applications of biosamples and showcase the results of an ongoing survey of biospecimens from twin registries and studies from around the world. *Conclusion:* In summary, this presentation will provide guidance for those wishing to collect biosamples from twins and provide information for those wishing to optimise the use of existing biosamples.

HOW CHIMAERIC ARE DIZYGOTIC MONOCHORIONIC TWINS?

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Introduction: In recent years, we and other have reported monochorionic dizygotic (MCDZ) twins, almost exclusively following treatment with assisted reproductive technologies (ART). We present a further case report with an analysis of chimaerism at multiple time points and tissues. *Materials and Methods:* Twins were conceived after ovarian stimulation without IVF. Monochorionic diamniotic (MCDA) twins were diagnosed by ultrasound early in gestation. At 28 weeks gestation she developed twin-twin transfusion syndrome (TTTS) and male-male twins were delivered by cesarean section at 29 weeks. Histological examination of the placenta confirmed MCDA placentation with no other pathological features. Despite the clear evidence of monochorionicity, the twins' parents were unable to reconcile the presumed diagnosis of monozygosity with their sons' significantly discordant physical features as infants. Commercial zygosity testing suggested dizygosity. Chimaeric twins were suspected and appropriate investigations were arranged. A 12-marker microsatellite test was performed on DNA buccal tissue

from both twins; SNP microarray was used to genotype saliva and buccal DNA. *Results:* Buccal DNA confirmed dizygosity; only four loci were shared by the twins. SNP microarray of saliva collected at two independent timepoints showed chimaerism throughout the genome in both twins. Genotype comparison between twins showed different regions of parental meiotic recombination. This supports a dizygotic twinning event and suggests infiltration of saliva from haematopoietic stem cells from both twins as a result of extensive blood sharing in utero in association with placental vascular anastomoses and associated TTTS. SNP microarray on buccal samples showed normal genotyping profiles for both twins further confirming dizygosity. Current investigations are focusing on other tissues to further investigate this hypothesis. *Conclusion:* This case study represents a further, albeit rare, exception to the rule that 'monochorionicity guarantees monozygosity'. Almost all cases of MCDZ twins have involved treatment with ART, often with microinjection techniques and, in two cases, by spontaneous fertilisation following ovarian stimulation. Our data suggest that fusion of the trophectoderm in DZ twins early in gestation can lead to monochorionicity and, sometimes to its associated complications including TTTS. Blood chimaerism must involve transfer and subsequent proliferation of hematopoietic stem cells, which could infiltrate into the oral cavity. Further studies on tissues other than blood and saliva need to be carried out to exclude somatic chimaerism in tissues other than blood. Knowledge of chimaerism is of paramount importance when counseling parents about similarities and differences in health and wellbeing within such twin pairs.

CAN WE DO MORE TO HELP PARENTS OF NEWBORN TWINS UNDERSTAND ABOUT ZYGOSITY AND CHORIONICITY?

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Background: For many years, twin research has provided insights into the genetic and environmental origins of health and disease. Such studies have relied on estimates of zygosity based on sex and chorionicity. However, the extent to which twins and parents of twins are informed about and understand zygosity is unknown. *Aims/Hypothesis:* To ascertain the levels of zygosity knowledge held by adult twins and parents of twin children. To determine the basis of zygosity knowledge and to understand what zygosity knowledge means to twins and their families. *Materials and Methods:* At the 2012 Australian TwinsPlus Festival we offered zygosity testing for twins and parents of twins who were at all unsure about their zygosity status. Buccal DNA was sent to the Australian Genome Research Facility for a 12-marker short tandem repeat zygosity test and results (monozygotic or dizygotic) were fed back to participants. Two short questionnaires were completed by participants; one at the time of providing the buccal sample and another after they received the zygosity results. These questionnaires were completed by adult twin participants and parents of child twin participants. Qualitative and quantitative information was collected about the basis of their zygosity knowledge (e.g. doctors, observations), as well as the importance and impact of the knowledge. *Results:* Of 125 pairs from which a cheek swab was provided, more than 90% were found by DNA testing to be monozygotic. One in five of the tested twins had incorrectly thought they were dizygotic. One in three said that they had received misinformation from medical professionals. Incorrect calls were based on the false assumptions that two placentas meant dizygotic twins and/or that monozygotic twins always look identical. Parents and adult twin pairs alike said that it was very important for them to know the true zygosity and many were extremely surprised at the results. The reasons most frequently provided regarding the importance of zygosity knowledge were: (1) for certainty; (2) for identity; (3) for health reasons. *Conclusion:* Zygosity knowledge among twins and parents of twins needs to be improved. We recommend that: (1) all parents of newborn twins in Australia should be provided with written information on the twins' chorionicity and zygosity wherever possible; (2) that all same-sex twin pairs should be recommended to have zygosity tests unless medical professionals provide written evidence that twins shared the same placenta; and (3) twins and parents of twins should have easy access to details how to be zygosity tested.

TWIN MYTHOLOGY IN THE AMERICAN CONTINENT

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Objective: To describe twin myths in some of the aboriginal tribes of the American continent. *Materials and Background:* The theme of twinship in mythology is prevalent worldwide. Western Hemisphere twin myths are less acknowledged. In North America, twin myths have been inherited thru different raconteurs and are present in the native Indian tribes of the Yuma (Colorado River Valley), the Skidi Pawnee (Nebraska), the Navajo (Arizona, New Mexico) and the Winnebago (Wisconsin, Minnesota, Iowa, Illinois), among many others. In Mesoamerica, the Maya tribe of the Quiches (Guatemala, southern Mexico) chronicled the adventures of their mythological twins in the text *Popol Vuh*. Their names were Hunahpu and Xbalanque and are given the honorific title of 'Hero Twins'. In South America, the Yekuana tribe (Venezuela, Brazil) and the Canelos - Quichua tribe (Ecuador, Peru) named their Hero Twins Iureke and Shikiemona, while in the Kamayura tribe (Brazil Amazon Basin) their names are Kuat and Iae. *Results:* Aside from the honorific titles, there are likenesses and dissimilarities among the myths. The Yuma tribe (southwest Arizona) have a myth called 'The Good Twin and the Evil Twin'. In contrast, in the Maya both twins are good. The notion of the twin's magical conception is shared by some myths. Xquic, mother of the Maya Hero Twins, gets pregnant when a desiccated head in a calabash tree spat on her hand. In the Kamayura, the twins incubate and emerge from a calabash gourd. In the Skidi Pawnee myth of 'Long Tooth Boy', the belief is that a twin emerges from a placenta that has been thrown away after the death of the laboring mother. The fact that twins are not identical is well described in some myths. The Maya Hero Twins have specific skin markings. Hunahpu has either a single black spot or three dots on his cheek and large spots on his body. In contrast, Xbalanque has jaguar-like spots on his lower face and patches of jaguar pelt on his arms, legs and back. In the Winnebago, the older twin is larger but less dominant than his younger brother. The common themes of the myths include: twins are heroes, warriors and ball players. They have miraculous powers such as the ability to resurrect the dead and to be reborn after their own death. Astronomically, they are related to the Sun, the Moon, Venus or some Stars. The Twins are avengers of a relative's death. In both the Maya and Winnebago myths, a character is beheaded and the Hero Twins recover the head. In 2009, a team of archeologists uncovered a sculptural frieze dated approximately 200 BC in the city of EL Mirador in a Northern Guatemalan rainforest. It depicts the Maya Hero twins swimming from the Underworld with the decapitated head of their father. *Conclusion:* Twin mythology, in the aboriginal tribes of North, Central and South America is a central, universal and recurring theme.

RELATIONSHIP BETWEEN PRE-DIABETES AND SLEEP DURATION IN MEN FROM THE DANISH GEMINAKAR TWIN COHORT

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Introduction: Sleep duration may be independently related to obesity and type 2 diabetes mellitus risk and the relation may be U-formed. However, only a few studies have been performed on the relationship between sleep duration and pre-diabetes, which is a high-risk state for diabetes. The purpose of this study was to examine the association between sleep duration and pre-diabetes as defined by glycosylated haemoglobin (HbA1c) between 5.7 and 6.4 % in a cross-sectional study of twins. *Materials and Methods:* This study uses data from the follow-up study of the longitudinal GEMINAKAR twin cohort. In the original study, a total of 756 complete twin pairs (aged 18–67 years) were recruited between 1997 and 2000 from the nationwide population-based Danish Twin Registry. They were initially free of cardiovascular disease and diabetes, and followed up approximately 12 years later (2010–2012). At follow-up, 1,139 subjects (>79%) agreed to participate, of which 1,119 underwent a clinical examination and a questionnaire survey concerning physical health and health-related behaviour. In total, 1,003 subjects had full information on sleep duration (estimated from the Pittsburgh Sleep Quality Index), HbA1c % and various covariates available for the present study. *Results:* Multiple logistic regression was used to examine the association between sleep duration (≤5 h/n, >5-6 h/n, >6-7 h/n, >7-8 h/n, >8 h/n) as the independent variable and pre-diabetes status as the dependent variable. Non-linear tests for trends were used to assess the potential U-shaped relationship between sleep duration and pre-diabetes status. After adjustment for age, current smoking and BMI, sleeping ≤ 5 h/night was associated with pre-diabetes in men (odds ratio 3.52, 95% CI 0.94-13.18 vs. >6-7 h; $p = .061$) but not in women. The relationship seemed U-shaped but this did not reach statistical significance. *Conclusion:* Findings suggest that short sleep duration is more strongly associated with pre-diabetes than >6-7 hours per day. This may indicate that inadequate sleep impairs glucose control in the short term, which is associated with an increased risk of developing diabetes. However, due to the small groups the conclusion is very cautious and as this is a cross-sectional study, the temporal relation between sleep duration and pre-diabetes could not be examined.

GENERALIZED ANXIETY DISORDER: A TWIN STUDY OF GENETIC ARCHITECTURE, GENOME-WIDE ASSOCIATION AND DIFFERENTIAL GENE EXPRESSION

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Introduction: Generalized Anxiety Disorder is the most prevalent anxiety diagnosis and affects approximately 5% of the adult population. Anxiety symptoms are often combined with an assortment of somatic and psychological complaints, such as sleep disruption, irritability, autonomic arousal, restlessness, fatigue and difficulties in concentrating. GABAergic neuronal transmission within the limbic system has shown to be the main factor in eliciting anxiety-like symptoms. A clinical metric used to measure anxiety is the Anxiety Sensitivity Index (ASI), which attempts to encompass and objectify the overall psychological and somatic symptoms of GAD. *Materials and Methods:* ASI data was collected from participants previously recruited from the TwinsUK resource. The 730 participants were comprised of 143 MZ and 222 DZ twin pairs and ranged from 38.7 to 84.7 years of age. RNA-seq data from LCL tissue was examined in a subset of the samples containing MZ twins discordant for ASI with one twin with an ASI <10 (control) with a sibling with an ASE score higher 15 points higher (case). 25 discordant MZ pairs were identified which matched the criteria. A linear mixed effect model was fitted for the scaled exon values of LCL tissue using the R package lmer. Also a GWAS using ASI as the phenotype was run using the program GEMMA, taking age as a covariate and incorporating the family structure of the twins into the analysis. *Results:* A heritability analysis of the ASI score using the ACE model estimated h2 as being 0.42. The GWAS analysis presented numerous SNPs of suggestive significance (4.16×10-8-9 x10-8) occurring within the coding region of the RBFOX1 gene. Additionally, the MZ twin discordance analysis showed statistically significant higher expression (1.26E-07 and 2.94E-07) respectively of exons 5 and 6 in the ITM2B (BRI2) gene for the anxiety cohort. *Conclusion:* ITM2B is strongly associated with British and Danish Familiar Dementia diseases. Neuronal degeneration is caused by a point mutation at the stop coding of ITM2B creating longer ABri peptide, causing the toxic amyloid fibrils to accumulate in the brain. Amyloid fibrils have previously been shown to deposit in the limbic system, which will potentially cause GABAergic neuronal death and contribute to the onset of anxiety. RBFOX1 also has shown a association with the anxiety pathology by regulating the splicing change of Gabrg2 responsible for functionality of the GABA(A) receptor. While GAD shows comorbidity with a variety of psychiatric and neurodegenerative disorders, our analysis suggest a novel etiology for the condition, with genetic variants being a significant risk factor.

THE CREATIVE PROCESS AND IDENTITY OF TWIN ARTISTS IN CONTEMPORARY ART

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Introduction: Twins have been studied in all areas of science; however, there is a gap in the equivalent to this research in the area of contemporary art. We were interested in finding out how the biological, genetic and environmental condition affects twin artists in relation to the discourse they present, whether it is a unique discourse because they are twins, and whether they all share common features. *Materials and Methods:* Our in-depth study of the subject is based on three methodological procedures. First, twin artists were directly contacted and then interviewed utilising a standard questionnaire. Second, existing information on twins was examined through a review of specific literature on twins and of artistic theory literature and through visits to artists' personal websites and exhibitions. Third, the quantitative analysis was carried out on a database of twin artists and statistics. *Results:* As a result we have observed that most of the 103 cases of twin artists are MZ (75.7%) and have chosen the same profession (91%) as opposed to DZ twins (10.6%) who do not work so frequently in the same profession (54.6%) with evidence of a genetic predisposition. The type of work, however, which we have divided into joint (MZ 69.2% and DZ 27.3%) and individual (MZ 30.8 % and DZ 72.7%) is also shaped by environmental factors, creating a correlation between twin typology and method of work. *Conclusion:* The results have enabled us to observe that the fact of having been born twins affects art, and therefore, being twins is influenced by biology, genetics and the specific environment surrounding them. Thus, the art created by twins becomes part of the contemporary movement of research on personal identity where being a twin is an identifying mark that influences both the work itself and its execution.

MONOAMNIOTIC TWINS: OUTCOME OF 41 CONSECUTIVE CASES IN A SINGLE INSTITUTION

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Introduction: Monochorionic monoamniotic (MCMA) twins are at high risk of perinatal death, with perinatal mortality traditionally reported to be approximately 15%. Potential complications are numerous and include those common to other twin gestations, including pre-eclampsia and premature labour, and complications specific to monochorionic twin pregnancies, including twin reversed arterial perfusion (TRAP) sequence and twin-twin transfusion syndrome (TTTS). Cord entanglement and the potential for occlusion is a unique characteristic of MCMA twin pregnancies that can result in single or double fetal demise. *Materials and Methods:* A retrospective cohort analysis of all MCMA twins managed in our institution from 2003 to 2013 was performed. Our ultrasound database was used to identify the MCMA twin pregnancies. All pregnancies had the diagnosis confirmed by histopathology postnatally. Perinatal outcomes were determined from the hospital record, private doctors' medical records and the hospital database. All patients born in and after 2006 were admitted to hospital for inpatient monitoring at 26 weeks gestation. Cardiotocography was performed for at least 1 hour, three times daily. Prophylactic corticosteroids were administered and delivery was planned by cesarean section at 32 weeks. *Results:* 41 patients were diagnosed with MCMA twins from early pregnancy ultrasound prior to 13 weeks gestation. Maternal age ranged from 17 to 43 years. Fifteen were primiparous and 26 multiparous. There were two acardiac twins and two sets of conjoined twins in this cohort. Five pregnancies were terminated prior to 20 weeks for maternal request. Three pregnancies miscarried spontaneously prior to 20 weeks: preterm prelabour rupture of membranes and antepartum haemorrhage (1), TTTS (1) and cord occlusion (1). Twenty-four pregnancies proceeded beyond 20 weeks gestation. Ten patients required an emergency cesarean section for an abnormal CTG. Fourteen were delivered by planned elective cesarean section at 32 weeks. If discordant anomalies were excluded, there were no fetal deaths after 20 weeks gestation. The single neonatal death was on day 4 of life as a consequence of transposition of the great arteries. The overall perinatal mortality rate was 2.1%. The non-anomalous perinatal mortality was zero. *Conclusion:* MCMA pregnancies are complicated at all gestations. TTTS is rare, fetal anomalies are common, and cord entanglement is universal. Our findings support the previously described low perinatal mortality associated with an intensive monitoring protocol.

OBSESSIVE-COMPULSIVE SYMPTOMS: GENOME-WIDE ASSOCIATION AND BEYOND

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Introduction: Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric disorder that is characterized by recurrent, persistent and intrusive anxiety-provoking thoughts or images (obsessions) and subsequent repetitive behaviors (compulsions) performed to reduce anxiety and/or distress caused by the obsessions. From a recent meta-analysis of twin studies, which estimated the heritability of Obsessive–Compulsive (OC) symptoms at 40%, it is clear that genetic factors are important in the etiology of OC symptoms. Molecular association studies have thus far not yielded consistent results, though we recognize that sample sizes were not large. Therefore, recent collaborative efforts have aimed at increasing sample sizes and at replication of results in discovery cohorts. We aimed to contribute to gaining further insights into the genetic basis of OC symptoms by performing a series of analyses in a homogeneous, population based sample registered with the Netherlands Twin Registry (NTR). *Materials and Methods:* First, a Genome-Wide Association Study (GWAS) was performed on 6,931 subjects registered at the NTR, to search for common single nucleotide polymorphisms (SNPs) responsible for predisposition of OC symptoms. Second, for the identification of genes associated with OC symptoms, gene-based tests were performed using GATES as implemented in the KGG software; this combines the effects of all SNPs in a gene into a test statistic and considers the association between the trait and the genes instead of all markers individually. By complementing GWAS with gene-based testing, a gene-centric result is obtained estimating the relative importance of each gene. Furthermore, confounding factors such as Linkage Disequilibrium (LD) structure and gene size are corrected for. Combining these two approaches is ideally suited for pathway analysis to better interpret the findings from GWAS. *Results:* One SNP (rs8100480), located within the MEF2BNB gene, was positively associated with OC symptoms ($P = 5.6 \times 10–8$). Gene-based testing resulted in 4 significant associated genes, all located in the same chromosomal region (19p13.11); RFXANK ($P = 5.6 \times 10–7$), MEF2BNB ($P = 9.7 \times 10–7$), MEF2BNB-MEF2B ($P = 1.29 \times 10–6$) and MEF2B ($P = 8.1 \times 10–6$). *Conclusion:* Genes significantly associated in this study are expressed in the brain and involved in development and control of immune system functions (RFXANK) and the regulation of gene expression of muscle specific genes (MEF2BNB). Interestingly, the MEF2BNB gene also showed a suggestive association with OCD in a previous gene based study using a case-control design. This gene therefore might play an important role in the development of OCD, and needs further study.

MONOZYGOTIC TWINS AFTER ASSISTED REPRODUCTION: A CHANGE IN CHORIONICITY

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Introduction: The present study aims at a better evaluation of the frequency and placentation of monozygotic (MZ) twinning in relation to assisted reproduction. The population-based data collected since 1964 by the East Flanders Prospective Twin Survey (EFPTS) provides accurate zygosity and chorionicity determinations for almost all pairs of twins born in the province. Furthermore, it distinguishes between spontaneous cases and those resulting from assisted reproductive techniques (ART) or the use of ovulatory drugs alone (non-ART). *Materials and Methods:* The EFPTS cohort (1976–2011) comprised 4,662 (64%) naturally conceived and 2,477 (34%) medically conceived twin pairs, including 1,111 (15%) twin pairs born after ovarian stimulation and 1,366 (19.0%) twin pairs born after in vitro fertilisation or intracytoplasmic sperm injection. *Results:* Women who had had subfertility treatment were on average older ($p < .001$) and less likely to have had a child previously ($p < .001$) than mothers in the natural conception group. As expected, the zygosity distribution is totally different in spontaneous and iatrogenic twins: 54% DZs in the natural conception group and 92%

among medically conceived twins ($p < .01$). Furthermore, among MZ twins the ratio of monochorionic (late embryo splitting) versus dichorionic pairs (early embryo splitting) is higher in the ART group as compared to the non-ART and spontaneous group in general: 86% (38/44) monochorionics in twin pairs born after in vitro fertilisation or intracytoplasmic sperm injection, 69% (58/83) in the twins born after ovarian stimulation alone and 66% (1261/1930) in the naturally conceived twins ($p < .01$). This surely needs further investigation and attention because no changes in the ratio have been observed previously. The increased risk of monochorionic twinning associated with infertility treatment is not merely of academic interest as the outcome of twin maternities is markedly affected by zygosity, and more specifically chorionicity. *Conclusion:* The data of the population-based, prospective survey of multiple births in East Flanders, Belgium, show that among MZ twins born after assisted reproduction, the ratio of monochorionic versus dichorionic pairs is higher compared with spontaneous twins and twins born after ovarian stimulation alone.

EARLY-LIFE NUTRITIONAL DETERMINANTS OF CHILDHOOD BMI

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Introduction: High protein intake and rapid weight gain during the sensitive period of early infancy have been proposed to influence the development of obesity in later life. We aimed to: (1) investigate the associations between early-life nutritional factors, current dietary habits, and body mass index (BMI) at age 9; (2) apply a trivariate Cholesky decomposition model to estimate the genetic and environmental contributions to the covariance of rapid weight gain in early infancy and later childhood BMI at age 5 and 9; and (3) test whether early life or current nutritional factors modify the heritability of obesity at age 9. *Materials and Methods:* We analyzed longitudinal data from 748 (360 boys, 388 girls) 9-year-old children (314 MZ, 434 SSDZ) from the population-based Quebec Newborn Twin Study. Maternal hypertension, diabetes and gestational age of the child were taken from medical records. Infant weight gain during the first 5 months of life was asked by questionnaire. Dietary intake at age 9 was estimated by two multiple-pass 24-hour dietary recalls with the child and one parent. *Results:* Among early life nutritional factors, rapid weight gain in early infancy was positively and breastfeeding duration inversely related to later childhood BMI. Early introduction of solid food and cow's milk were related to increased childhood BMI in boys. Among current dietary factors, total energy intake, energy from protein, refined grains, potatoes, high-fat meat and soft drinks were associated with increased childhood BMI. The heritability estimates for growth and BMI were: 59% (95% CI: 42–80%) for infant weight gain during the first 5 months of life, 80% (73–85%) for BMI at age 5 and 81% (75–86%) for BMI at age 9. Genetic factors that associated with infant weight gain were partly overlapping with those that influenced BMI at age 5 ($rg = 0.42$) and age 9 ($rg = 0.28$). The genetic contribution to variation in BMI at age 9 was higher in children who were born preterm, children whose mothers had hypertension during pregnancy, children who did not adhere to recommended feeding practices in early infancy and children who consumed more energy from protein at age 9. *Conclusion:* Maternal hypertension, early life nutritional factors and energy intake from protein are associated with childhood BMI at age 9 and may modify the action of the genes predisposing to childhood obesity.

THE INFLUENCE OF GENERAL ANESTHESIA AND SURGERY IN OLD AGE: A TWIN STUDY

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Introduction: There is a pronounced variation in level of cognitive function and rate of cognitive decline in late life. Results from smaller human and animal studies suggest that exposure to anesthesia may be a risk factor for cognitive impairment. Using a twin design, the objective of the present study was to examine whether exposure to anesthesia and surgery is associated with level of cognitive function in middle and old age. *Materials and Methods:* The study is based on two population-based surveys comprising 8,503 Danish twins aged 45–102 years at study intake during 1995–2001. Through linkage to the Danish National Patient Register, we obtained information on surgeries performed in hospitals in Denmark from 1977 and until study intake. Four exposure groups were defined based on type of surgery (major, minor, knee and hip replacement, other). A cognitive test battery consisting of five brief cognitive tests was used in the study, and a composite cognitive score was calculated. Linear regression models adjusting for gender and age at examination were used. To address genetic and shared environmental confounding, intra-pair analyses were performed in a sample of 87 monozygotic and 124 dizygotic same-sex twin pairs who were discordant for anesthesia and major surgery exposure. For this analysis, the proportion of pairs in which the co-twin who had been exposed to anesthesia and major surgery and also had the lowest composite cognitive score was calculated. This proportion was compared to the null hypothesis of equality (50%/50%) by using the exact binominal test. *Results:* Significantly lower cognitive scores were found for twins with at least one major surgery compared to those with no surgery before study intake (mean difference -0.28 [95% CI:-0.48;-0.06]) corresponding to about 10% of an *SD*. No significant differences were found for twins with other surgeries under general anesthesia or for twins with minor surgeries compared with those who received no surgery. Twins with knee or hip replacement surgeries tended to have higher composite cognitive score than those who had no surgery (mean difference 0.34 [95% CI:-0.18;0.86]). In the intra-pair analyses, the exposed co-twin had the highest composite cognitive score in 51% [95% CI: 0.42;0.56] of the pairs. *Conclusion:* Both unpaired and intra-pair analyses of a large sample of middle-aged and elderly twins found no convincing evidence for a substantial effect of general anesthesia on cognitive abilities, as only a modest difference was detected according to exposure to major surgery. Future unpaired and paired longitudinal studies will be conducted to assess cognitive decline in more detail and will include age at exposure and the impact of time after surgery.

FAST FOOD CONSUMPTION AND BODY MASS INDEX: A TWIN STUDY

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Introduction: Over one-third of adults and 17% of children and adolescents in the United States are obese. Several lifestyle behaviors are linked to obesity, including poor dietary habits such

as the increased consumption of fast-food meals over the past few decades, which has closely mirrored the rise in obesity prevalence in the United States. The objective of this study was to determine the association between BMI and fast food consumption among a sample of adult twins. We hypothesized that fast-food consumption was independently associated with BMI both between and within adult twins. *Materials and Methods:* This cross-sectional, secondary data analysis included 698 same-sex pairs, using data from surveys collected 2006–2011. The primary outcome was continuous BMI (kg/m^2) derived from self-reported height and weight. The primary exposure was fast-food consumption, collected using the following question: 'During the past 4 weeks, how many times in a typical week did you eat a meal at a fast-food restaurant such as McDonalds, Burger King, or KFC?'. Answers were recorded as 0, 1–2, 3–4, and 5 or more times per week. Covariates included age, sex, race, income, education, physical activity, and neighborhood density of fast-food restaurants. We used methods described by Carlin et al. to test associations between fast food consumption and BMI in twins; specifically, generalized estimating equations (GEE) to estimate the population-averaged (between-twin) effect and within-pair differences. *Results:* Variance in fast-food consumption had no additive genetic component and was explained by the shared (37%) and unique environment (63%), whereas variance in BMI was explained by additive genetics (83%) and the unique environment (17%). In the unadjusted GEE model, a one-unit greater increase in fast-food consumption was associated with a 0.62-unit greater BMI (95% CI: 0.35–0.89). Associations were attenuated when adjusted for covariates in sequential models; however, regression coefficients remained significant ($ps < .05$). In contrast, there was no overall association between within-pair differences in fast-food consumption and within-pair differences in BMI in any model ($ps > .05$). However, the association between within-pair differences in fast-food consumption and BMI in an unadjusted model was significant within-DZ twins (0.65, 95% CI: 0.02–1.29). The association remained significant when adjusting for income and education ($p < 0.05$), but was attenuated and no longer significant in subsequent models once physical activity and fast-food restaurant density were sequentially included ($p = .065$ and .051, respectively). *Conclusion:* Family-level factors play an important role in the association between fast-food consumption and BMI. This suggests that any observed association between fast-food consumption and BMI is not causal.

COMPLICATED MONOCHORIONIC PREGNANCIES, FETAL THERAPY AND NEUROLOGICAL INJURY.

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Objectives: (1) To evaluate the presence of cerebral injury in the survivor twin after intrauterine death of the co-twin in monochorionic pregnancies (MC) complicated by Twin-to-Twin Transfusion Syndrome (TTTS) or selective intrauterine growth restriction (sIUGR), comparing spontaneous fetal loss versus demise after therapeutical procedure: fetoscopic selective laser ablation of placental anastomosis or umbilical cord occlusion(UCO). (2) To analyze the role of prenatal Neurosonography (NS) and Magnetic Resonance Imaging (MRI) in the evaluation of brain injury in these cases. *Materials and Methods:* Retrospective study of MC pregnancies complicated by TTTS or sIUGR and intrauterine death of one twin (spontaneosly or after therapeutical procedure). Ultrasound follow-up and also MRI of the survivor 4 weeks after intrauterine fetal demise were made in all cases (July 2011–December 2013) *Results:* During the study period 112 MC pregnancies were followed up in our Unit.We studied n cases (6 TTTS and 3 II-III type sIUGR) with intrauterine death of one twin. In 3 of the cases the fetal loss was spontaneous. Of the 6 cases in which the fetal demise occurred after therapy, 2 patients had undergone fetoscopic selective laser ablation of placental anastomosis and 4 of them UCO. Cerebral abnormalities were detected in only one case: type III sIUGR with spontaneous death of one twin in week 18. NS and MRI showed similar findings (ventriculomegaly, destructive white matter lesions and microencefaly). Parents requested a voluntary interruption of pregnancy. No cerebral lesions were observed by fetal NS, fetal MRI or neonatal MRI in the surviving co-twin when intrauterine therapeutical procedure had been undergone. *Conclusion:* The risk of cerebral damage in the surviving twin in MC pregnanciesis greater when the fetal demise is spontaneous than when it occurs after therapy. In our study, the diagnostic capability of NS and MRI was similar.

THE OUTCOME OF TWIN PREGNANCIES DISCORDANT FOR TRISOMY 21

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Introduction: Trisomy 21 is associated with increased risks of miscarriage, fetal growth restriction, preterm delivery and fetal demise. The management of twin pregnancies discordant for trisomy 21 is dependent on the gestation at diagnosis, chorionicity, and parental preference. Pregnancies that are concordant are almost always terminated. There is limited available data on discordant pregnancies that continue. *Materials and Methods:* The Royal Women's Hospital, Melbourne, is a tertiary referral centre with a dedicated multiple pregnancy unit. Cases were retrospectively identified through a comprehensive hospital database search from January 2000 to December 2011. Aneuploidy screening was by either nuchal translucency alone or with combined first trimester maternal serum screening and nuchal translucency, depending on the gestation at which the patient was seen. Diagnostic testing was offered based on high-risk first trimester screening, fetal anomaly or advanced maternal age. *Results:* Our experience with the management of 15 cases in 1,839 twin pregnancies over a 12-year period is described. *Conclusion:* Twins discordant for trisomy 21 are rare. This case series highlights that there is the possibility of discordance for aneuploidy even in monozygotic twins. This may be due to post-zygotic non-dysjunction. Amniocentesis should be strongly considered in these cases given the possibility of a false negative result from chorionic villus sampling. The decision to proceed with selective termination of the affected twin has greater complexity in non-lethal conditions such as trisomy 21 and it is not always a parent's wish to avoid an affected child. The terminations performed in this series were later than recommended gestation, reflective of the difficulty in the decision-making process. Pregnancies that continue with a trisomy 21 affected fetus are at risk of polyhydramnios and premature labour. They are also at risk of selective growth restriction; however, this was surprisingly just as likely to occur in the non-affected as the affected fetus.

OUTCOME OF MULTIPLE PREGNANCIES AT MISURATA TEACHING HOSPITAL

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Introduction: Data of multiple pregnancies were analyzed in comparison to other studies to find out whether maternal and perinatal morbidity and mortality and neonatal morbidity are influenced by mode of delivery. *Materials and Methods:* Medical records of all women with multiple pregnancies who delivered at the Misurata Teaching Hospital, Libya, over a period of 24 months (January

2012–December 2013) and at ≥32 weeks, were reviewed retrospectively. Baseline characteristics, neonatal and maternal outcomes were documented according to the planned mode of delivery, including maternal and gestational age at delivery, parity, birth weight, 5-min Apgar scores, birth trauma and serious neonatal morbidity, blood loss postpartum, genital tract injury, body temperature, and serious maternal morbidity during the first 28 days postpartum. Statistical analysis performed using SPSS package. *P*-value was considered to be significant if <.05. *Results:* Total number of deliveries was 13,998. The number of multiple deliveries was 258: twins (241), triplets (15) and quadriplets (2). The incidence of twin pregnancy was 17.2/1,000 deliveries (1.72%), which is in agreement with many studies, although ART and infertility management has increased the incidence of multiple pregnancies. The majority of cases with multiple pregnancies were <35 years, although the marriage age is still younger than other countries. Most of the primigravidae with multiple pregnancies were delivered by cesarean sections(CS; 72.2%; $p < .05$). Para1-Para5 patients with twins showed a significant increase in the number of vaginal deliveries (67%). Of the twin pregnancies delivered after 37 weeks (69%), 31% were preterm ($p < .05$). Only one twin baby died during a planned vaginal delivery. An emergency CS for both twins was performed in 16 women; indications were fetal presentation, distress, preeclampsia and failure to progress. Two patients in those delivered by CS needed a relaparotomy for hemorrhage. There were no significant differences in maternal morbidity, mortality and morbidity in the neonates between CS and vaginal birth apart from risk of blood transfusion. All cases of multiple pregnancies with IUFD were delivered vaginally. *Conclusion:* Our results do not support an elective cesarean section for twin gestations of ≥32 weeks as no significant differences in maternal and perinatal morbidity and mortality and neonatal morbidity were found between twins born by cesarean sections and those born vaginally.

A META-ANALYTIC TWIN APPROACH TO UNRAVELING THE COMPLEX ETIOLOGY OF MULTIPLE SCLEROSIS

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Introduction: Most published twin studies of multiple sclerosis (MS) are affected by a low statistical power, and thus are inconclusive with regard to the impact of genes and environment on individual liability to the disease. In particular, high uncertainty exists about whether shared environmental factors are of relevance in disease etiology. In this context, a meta-analysis of available evidence from previous efforts would allow deriving quantitative summary estimates of heritability and of shared and unique environmental components of MS, and disentangling their relative contributions with a reasonable degree of confidence. *Materials and Methods:* We used a structured MEDLINE search to identify all published twin studies of MS. Then, by including only those studies that met the minimal criterion of systematic case ascertainment, and by considering the most recent among multiple reports in the same populations, we selected eight studies for the analysis (from France, UK, Canada, Denmark, North America, Italy, Finland and Sweden). Of these studies, three (from Italy, Finland and Sweden) had performed quantitative genetic modeling; one (from Sweden) had also applied an extended twin-sib model, while the remaining studies were limited to the classical twin concordance estimation. We conducted a biometric multi-group analysis under the liability-threshold model by taking account of the study-specific ascertainment strategies and the population-specific prevalence rates of MS. We obtained study-specific and summary estimates of: (1) tetrachoric correlations in monozygotic (MZ) and dizygotic (DZ) twin pairs, that we interpreted within the assumptions of the twin design; (2) additive genetic, shared and unique environmental proportions of MS liability variance, that we also subjected to heterogeneity testing between studies. *Results:* Study-specific tetrachoric correlations in MZ and DZ pairs were consistent with a model including all three components of variance (i.e., additive genetic, shared and unique environmental) for all populations except Denmark and Sweden, for which shared environmental signatures were absent. The summary estimates of tetrachoric correlations were 0.71 (95%CI: 0.67–0.74) in MZ pairs and 0.46 (95%CI: 0.41–0.50) in DZ pairs, indicating substantial additive genetic effects and suggesting that moderate shared environmental influences may also come into play. Consistent with this correlation pattern, the biometric multi-group model provided joint estimates of 0.50 (95%CI: 0.39–0.61) for the heritability, 0.21 (95%CI: 0.11–0.30) for the shared environmental component, and 0.29 (95%CI: 0.26–0.33) for the unique environmental proportion of variance. We detected significant between-studies heterogeneity in variance components estimates. *Conclusion:* Our meta-analytic results from eight published twin studies of MS are consistent with a view of MS as a complex disease that originates from heterogeneous genetic and environmental influences. These results support the rationality of the continuing efforts to identify genetic factors that affect individual liability to MS. Most notably, a unifying evidence emerges from the different studies in favour of aetiological environmental effects of the shared type. This encourages future investigations aimed to shed further light on the actual role of non-heritable components, such as intra-uterine factors and shared exposures to climate, diet and infectious agents.

COMMON ETIOLOGICAL SUBSTRATES FOR ASTHMA AND RESPIRATORY ALLERGIES: A LESSON FROM ITALIAN TWINS

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Introduction: Asthma and respiratory allergies are common conditions throughout the human lifespan. They affect quality of life and may cause complications in subjects with severe concomitant pathologies. There is consistent evidence that these conditions aggregate within families and co-occur in individuals. Accordingly, previous twin studies have focused on the origins of the comorbidity, and have demonstrated that shared etiological factors, both genetic and environmental, play a key role. However, the biological process driving the effect of shared factors remains unclear. We aimed to investigate the common etiological substrates of asthma, hay fever and allergic rhinitis (to causes other than pollens), and to test alternative mechanisms underlying the shared etiology. *Materials and Methods:* Subjects in this study are all the twins enrolled in the Italian Twin Registry with available information on asthma and respiratory allergies. The study population included around 2,800 twins aged 3–72 years. Data on asthma, hay fever and allergic rhinitis were collected by a validated self-report questionnaire: subjects were classified as affected if they (or their parents) responded positively to questions on the lifetime occurrence of these diseases, and only for asthma a doctor diagnosis was additionally required. The questionnaire also encompassed sections on environmental and infectious exposures, perinatal factors and family history of atopy. We estimated disease prevalence rates in twins as individuals, and crude and age-adjusted tetrachoric correlations in twin pairs. Furthermore, we performed biometric structural equation modeling,

and compared two alternative models (Common and Independent Pathway) implying different pathways for the shared genetic and environmental influences on the syndromes; the biometric analysis was conducted on both the total population and the restricted subpopulation of twins below the age of 18. *Results:* Prevalence rates of asthma, hay fever and allergic rhinitis in our twins were in line with the values reported for the general population; in particular, asthma prevalence was higher in males compared to females, while that of hay fever and allergic rhinitis increased by age. Cross-twin/within-trait tetrachoric correlations supported additive genetic and unique environmental effects for each of the diseases, and suggested shared environmental influences only for asthma. Within-twin/cross-trait correlations indicated a substantial co-occurrence of the conditions at individual level. Cross-twin/cross-trait correlations were consistent with genetic factors shared by the syndromes. Age-adjustment did not significantly modify the correlation pattern. The Common Pathway compared to the Independent Pathway model better explained the observed correlations. According to this model, the heritability of the common latent factor was about 70%; furthermore, for each disease, a large proportion of the genetic variance was shared with the other syndromes. In the subpopulation below 18 years of age, the Common Pathway model still performed adequately, and provided a higher heritability (about 90%) for the common latent factor. *Conclusion:* Our results on a large twin population showed a substantial comorbidity between asthma, hay fever and allergic rhinitis, and pointed to shared genetic factors as major contributors to the comorbidity; moreover, the results suggested that a common heritable susceptibility may be a candidate mechanism for the shared etiology.

INNATE AND ACQUIRED INFLUENCES ON EMPATHY: A LARGE SURVEY ON ITALIAN TWINS

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Introduction: Empathy is a fundamental component of human social behaviour. Previous twin studies have investigated the genetic and environmental influences on several facets of social functioning, using different measurement tools for these facets. However, to our knowledge, no twin study has focused on empathy as assessed by the self-report Empathy Quotient (EQ) questionnaire. Therefore, we aimed: (1) to explore the relative contributions of genes and environment to individual differences in the EQ score among the general population; (2) to contribute to the validity assessment of this scale. *Materials and Methods:* Subjects were approximately 1,700 twins recruited within a large survey on all the twins aged 18–70 (about 5000 individuals) who had been enrolled in the Italian Twin Registry (ITR) over a period of nearly 12 years (from 2001 to 2012). The main objective of this survey was to investigate attitude towards biomedical research and willingness to donate biological material for research biobanks, and to explore the role of specific factors (including empathy) in shaping these aspects. Data on empathy were collected by the Italian version of the 40-item self-report EQ questionnaire. Total EQ score was derived for each twin and was subjected to statistical analyses, that are still underway. Most of the analyses are based on the twin method, and are aimed to estimate the heritability of the EQ score as well as the contributions of shared and unique environmental factors. Additional analyses aim to explore the association of the EQ score with attitude towards research and biological sample donation, and to assess the validity of the EQ questionnaire through the correlation with the Autism Quotient (AQ) (available from a previous ITR survey on a subsample of the same twins). *Results:* Mean values of the EQ score are in line with those commonly reported for the general population. As expected, females show a significantly higher EQ score compared to males. Initial twin analyses show a higher within-pair correlation for the EQ score in monozygotic compared to dizygotic pairs, suggesting a substantial heritability. In the final analyses, biometric model-fitting will be performed, and various hypotheses will be tested, including possible gender differences in the genetic and environmental components of the EQ score. As regards the association with the attitude towards research and donation, higher EQ levels seem to be associated with higher probability of unconditional agreement to donate biological material. Moreover, a preliminary inverse correlation with the AQ score confirms previous results on the divergent validity of the EQ questionnaire. *Conclusion:* There is a clear indication to further analyze the EQ score within the twin model, for a better understanding of the factors which contribute to the definition of this fundamental social life trait. Moreover, the results regarding the possible association of higher EQ levels with unconditional willingness to donate biological samples for research are of a certain interest for twin registries and their biobanking activities. Further investigations could contribute to the understanding of the role of the individual empathy profile which seems to underlie the willingness without condition (i.e., without personal interests) to donate biological material for research.

TRIPLET PREGNANCY: IS THE MODE OF CONCEPTION RELATED TO PERINATAL OUTCOMES?

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Introduction: Multiple pregnancy is associated with maternal and neonatal risk and monochorionicity further contributes to morbidity and mortality. Many triplets are conceived due to assisted reproductive technology (ART) and there is concern that ART-conceived triplet pregnancies are more complicated than those conceived spontaneously. This study aimed to evaluate triplet pregnancies managed over a 12-year period to determine if there were any differences in outcome based on the mode of conception. *Materials and Methods:* All triplet pregnancies over a 12-year period that reached at least 20 weeks' gestation and that were managed at the Royal Women's' Hospital, Melbourne, Victoria were identified. Maternal and neonatal outcomes were compared between ART conceived and spontaneously conceived triplets. *Results:* In the study period, 53 sets of triplets managed in our institution met the eligibility criteria. Twenty-five triplet sets were conceived by ART and 28 were conceived spontaneously. More ART conceptions resulted in trichorionic triamniotic (TCTA) triplets than did spontaneous conceptions ($p = .015$). There were no differences between ART and spontaneously conceived triplets for any of the maternal or neonatal complications studied. Trichorionic (TC) triplets delivered at a later gestation than other triplets: 32.1 (*SD* 2.9) versus 30.4 (*SD* 3.9) weeks ($p = .08$). TC triplets were significantly less likely to die than monochorionic or dichorionic triplets: 3/93 (3%) versus 13/66 (20%) ($p = .025$). *Conclusion:* Triplets conceived by ART are more likely to have TCTA placentation. Outcomes for triplets conceived by ART were similar to those of triplets conceived spontaneously. TCTA triplet sets had lower mortality rates than other triplet combinations. The current study offers reassurance to women who have conceived a triplet pregnancy as a consequence of ART: they have no increased risk of adverse maternal or neonatal outcomes as a consequence of their mode of conception. It further highlights the importance of chorionicity as a determinate of outcome in multiple pregnancies.

GENETIC AND LIFESTYLE FACTORS FOR LOW BACK PAIN IN BRAZILIAN TWINS: ESTABLISHMENT OF THE FIRST BRAZILIAN TWIN REGISTRY AS PART OF A GLOBAL NETWORK

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Introduction: The establishment of a twin registry in Brazil as part of a Global Network of Twin Registries has the potential to become a rich research resource for a variety of health fields. *Materials and Methods:* We are setting up the first Brazilian twin study investigating genetic and lifestyle factors of low back pain (LBP). Applying the methodology of the AUstralian Twin low BACK Pain study (AUTBACK), we are initially recruiting 300 twin pairs from Belo Horizonte. Twins participating in the LBP study will form the platform for the Brazilian Twin Registry. *Results:* The project has recently been granted funding and ethics. A pilot trial has been finalized, which showed study feasibility. Data collection started in March 2014. *Conclusion:* This is the first twin study in the field of LBP that will lead the implementation of the first twin registry in Brazil. The Brazilian Twin Registry will be an innovative resource and the opportunities for collaboration and data linkage are significant.

UNDERSTANDING THE EMOTIONAL CHALLENGES OF A TWIN PREGNANCY: HOW IT IMPACTS PARENTING AND IMPEDES INDIVIDUALITY

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Introduction: In contrast to a singleton pregnancy, most twin births are considered a high risk situation. Just the term 'high-risk' engenders anxiety and fear in the minds and hearts of most prospective couples. Throughout the pregnancy the numerous sonograms predict the weight, position, growth, and gender of each baby. The incidence of preterm labor and low birth weight weigh heavily upon expectant parents. Many have heard harrowing narratives about weeks and months in the NICU. It is my hypothesis that the triangular connection between mother and her two babies along with the twin-to-twin connection make it very difficult for parents to make separate attachments to each baby. The attachment to the pair appears powerful and exclusive, overriding the importance and necessity to connect to each baby as an individual. *Materials and Methods:* I will discuss various case histories that illustrate why it is so difficult for parents to separate their twins and spend alone time with each one, even when there is sufficient support to make such arrangements without undue stress or sacrifice. The importance of mentalizing each twin as an individual and to spend alone time with each baby is oftentimes denied or undermined by mothers and fathers. Parents of twins are often reluctant to give up the attention and narcissistic pleasure of being with both babies. Oftentimes the twin attention compensates for the lack of maternal satisfaction and frustration in trying to attach to two babies at the same time. *Results:* My first book, *Emotionally Healthy Twins,* describes parenting issues with twins, such as being aware that twins cannot be surrogate parents to one another and that parents cannot make their twins' lives fair and equal. My latest book,*The Same but Different: How Twins Can Live, Love, and Learn to be Individuals,* highlights some of the obstacles that twins confront as they get older. It is comprised of various case histories that illustrate what happens when twins are expected to be resilient individuals capable of separating to attend college, having other intimate relationships, and being able to handle a job apart from one's twin. Many psychological obstacles arise when twins are not raised as resilient individuals capable of being on their own socially, academically, or emotionally. The shame and struggle involved in working through this conundrum makes many adult twins depressed and angry — wanting to celebrate his success but unable to in the face of his/her twin's situation. Unlike sibling jealousy or competition, twin-related angst is complicated and embedded. If one gets a good job or has a successful relationship, one is happy but both feel depressed and guilty. The most poignant outcome of adult twins struggling to find their identify lies in their conflict about not being able to appreciate or value their own success if their twin is struggling or unhappy. The successful twin feels guilty and undeserving of his success in the face of his twin's negativity or depression. *Conclusion:* The twin pregnancy lays the groundwork for future growth and development. How parents formulate attitudes about Baby A and Baby B generates labeling and identity even before birth.

ENVIRONMENTAL INFLUENCES ON GENE EXPRESSION IN PERSONALITY FROM THE VIEWPOINT OF PEDAGOGICAL CASE STUDIES FOR TWINS IN JUNIOR AND HIGH SCHOOL

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Introduction: Despite having the same genetic makeup, MZ twins have their own distinctive personality. This is said to be affected by environmental factors, which can induce the expression of our genetic diathesis. This has led many researchers in the fields of anthropology and molecular biology to study twins, but there is little research in the pedagogic field yet, where it is also important to understand how the environment contributes to certain traits and the way our genes are expressed. The University of Tokyo Secondary School attached to the Faculty of Education, where the research was conducted, has been collecting data and case studies on secondary school students' academic ability, mentality and physical ability for 68 years since 1946. They covered 935 sets of MZ, DZ and triplets students in total, aged 12 to 18. We compared the similarity between twins in school educational activities and researched the effects of environment on personality of the individuals, using case studies. *Materials and Methods:* (1) Pedagogical case studies. There are two things we report here as one of the examples of the case studies. One is about the patterns of academic achievement of twins and the other is about perception of color between twins through drawing and coloring activities in Art classes. For over 30 years, we have had 10 MZ twin pairs every year offer academic achievement data for 6 consecutive school years. We analyzed the achievement fluctuation, calculating deviation from average of periodic examinations, such as Japanese, Social studies, Math, Science and English. (2) The features of Twin Studies in The University of Tokyo, Secondary School attached to the Faculty of Education. We are able to observe the same twins for 6 consecutive years in the same field, The University of Tokyo Secondary school. Each and every twin in our school takes the Twin Zygosity test (e.g., blood type, DNA). We are able to continuously research lifelong development after they graduate as well as their daily activities, interpersonal relationships, consciousness, and subjectivity during their adolescence in our school. We consider twins not as the subject of this research but as the subject of our educational practice The conductors of the case studies are the teachers in The University of Tokyo Secondary school, who are

well acquainted with the students, including the twins. *Results:* As a result of this analysis, we found that there are five patterns in achievement among monozygotic twins: (1) Parallel type, (2) Fluctuating difference type, (3) Non-difference type, (4) Reverse type, and (5) Decremental difference type. Through drawing and coloring activities in art lessons, we asked 10 MZ twin pairs and 10 DZ twins to draw pictures with the same theme under different situations, and we found that there were some similarities in brightness and chroma among DZ twins. However, the differences in hue and objects they drew increased as they grew older, in spite of the fact that twins tend to favor and choose the same colors when they draw pictures in their childhood. Considering that DZ twins did not show such a tendency, we can surmise two things from this, based on the assumption that drawing activities are related to cognitive abilities that are easily influenced by differences in the gene expression: (1) environmental factors affect hue and objects they draw; (2) environmental factors do not affect brightness and saturation in drawing activities. *Conclusion:* Although over the decade, studies of twins have provided numerical evidence of a contribution of genetic factors, the influences of education as an environmental factor on gene expression have yet to be revealed. It is generally thought that twins with the same genes and the same environment (i.e., the family and the school environment) such as the twins in our school, will have the same personality. Through these pedagogical case studies, however, we found that there is a significant difference between the MZ twins in personality, communication skills, emotional aspects, vocabulary ability and how they form relationships, and so on. On this basis, we suggest that this was caused by the differences of genetic expression, which are affected by slight differences in environmental factors — the psychological bond between twins, relationships with others, their position in a group and their sense of belonging. In conclusion, we can say that it is important to interpret the influence or the difference of environmental factors thst seemed to cause the difference in personality between MZ twins as this will lead us to reveal the influence of the educational environment and the effect of education as one of the environmental factors of gene expression on all students, including both twins and non-twins.

COMPLETION OF TWIN PREGNANCY: INDICATIONS AND MODE OF DELIVERY

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Introduction: The objective was to analyze end indications and mode of delivery in twin pregnancies. *Materials and Methods:* Gestational age at delivery, indication of termination of pregnancy, and the mode of delivery were used to retrospectively analyze twin deliveries at the Torrecárdenas hospital between March 2013 and March 2014. *Results:* During the assessment period, 3,125 deliveries were attended, with 64 twins. The mean gestational age at delivery (EGMP) was 36 + 2.4 weeks. 55.5% of births were preterm (<37 weeks). The main indications for termination of pregnancy were: elective for gestational age (37%) and birth year (34%); among the first in the dichorionic-diamniotic EMGP was 38.2 + 0.8 weeks and 37 + 0.3 on monochorionic-biamnióticas. 81% of births were preterm course (32–<37 weeks: 82.3%, 28–<32 weeks: 17.6%). As an indication of the route of delivery, 84% of cases were determined by the fetal position; cesarean delivery was initially noted in 60.4% and vaginal delivery in 39.6% (25 cases), although cesareans were completed 74.6% of cases. Of the 25 cases with initial indications for vaginal birth, 11 ended in cesarean, the most frequent failure of induction (5 cases) cause. *Conclusion:* More than half of the twin births in our sample were preterm. In the decision on the mode of delivery the most influential factor was the fetal position, with the main route of cesarean delivery in twin pregnancies, data that are consistent with those published.

PERINATAL CHARACTERISTICS OF A TWIN FETUS

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Introduction: The objective was to establish the characteristics of newborn twins in terms of position, weight, sex, and Apgar score. *Materials and Methods:* Twin births were reviewed retrospectively at the Torrecárdenas hospital between March 2013 and March 2014 and the following variables were analyzed: gestational age at delivery, fetal position, fetal sex, fetal birth weight, Percutaneous Endoscopic Gastrostomy (PEG) fetuses and Intrauterine growth retardation (CIR), Apgar score. *Results:* Of 63 twin deliveries, 55.6% were delivered before 37 weeks and 19% before 34 weeks. Cephalic position was found in both the first and second twin (77.8% and 49.2%); 63.5% were male. The mean birth weight was 2396 g for the first twin and 2278 g for the second ($p = .045$). In 55.6% of cases, the first twin had a higher birth weight than the second twin. We found 14.2% of fetuses PEG and 4.76% of fetuses CIR. The median Apgar score for both fetuses was 9/10, presenting a lower score in the first 5 minutes of the first 3.2% twins and 6.3% of the latter, while this was less than 7 at 5 minutes in 1.6% of first twins and 4.8% of the latter. *Conclusion:* The dominant position in both twins is cephalic, being more often found in the first. The first twins have a higher weight to the latter.

EPIDEMIOLOGY OF OUR MIDDLE TWIN PREGNANCIES

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Introduction: To determine the incidence of twin pregnancies in the last year in our country, their relation to assisted reproduction techniques (ART) and obstetric complications are presented. *Materials and Methods:* The twin births in the Torrecárdenas Hospital between March 2013 and March 2014 were retrospectively reviewed and the following variables were analyzed: maternal age, parity, ART, type of twin pregnancy and obstetric pathology. *Results:* 63 twin deliveries (2.01% of the total) were attended. Of these pregnancies, 43.45% used ART, while the majority (56.55%) were spontaneous pregnancies. The mean age was 31.4 years for spontaneous pregnancies ± 4.79 years, and 36.4 ± 6.17 years for ART ($p = .001$); 55.6% of women were nulliparous (38.1% secundiparous). For women using ART, 85.2% were nulliparous; 72.6% were dichorionic-biamnióticas, rising to 92.6% when ART was used. 27.4% were monochorionic-biamnióticas (7.4% in ART). With regard to obstetric pathology, 11.3% had gestational diabetes, 11.3% had hypertensive disease of pregnancy, and 9.6% APP. No significant changes were observed in pregnancies achieved by ART. *Conclusion:* ART has had a major impact on the incidence of twin pregnancies, mainly in dichorionic-biamnioticas. The obstetric pathology is increased in twin pregnancies.

PRENATAL DIAGNOSIS OF TWIN PREGNANCIES AND PERINATAL OUTCOME URETEROCELE

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Introduction: We describe a series of cases with prenatal diagnosis of twin pregnancies and perinatal outcome ureterocele. *Materials and Methods:* Retrospective study of two cases with prenatal

diagnosis of ureterocele between 2005 and 2013 were evaluated at the Fetal Medicine Unit of the hospital Torrecardenas through analysis of medical records. *Results:* Two cases of ureterocele and twin pregnancy were analyzed. The median gestational age at diagnosis was 26 weeks. The cases were isolated. In one, the fetal phenotype was female. The amniotic fluid was normal in one and oligoamnios was evident in the other. In both, hydronephrosis and megaureter were observed. Both showed duplication of the collecting system. Other associated findings were dysplastic kidney and megacystis appearance. In both, the diagnosis was confirmed and postnatal infants received immediate antibiotics and required surgical correction. *Conclusion:* Sonographic signs most frequently associated are hydronephrosis, megaureter and duplication of the collecting system. Less common are abnormal amniotic fluid and megacystis. Prenatal ultrasound detection of ureterocele is useful for the assessment, monitoring and early interventions newborn or fetus that can prevent severe renal damage and loss of function.

PULSATILITY AND RESISTANCE INDEXES IN UMBILICAL ARTERY DOPPLER MEASURED LOOP FREE AND PARAVESICAL CORD IN TWIN PREGNANCIES

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Introduction: Doppler umbilical artery (UA) is a central tool in the monitoring of high risk pregnancies; however, rates may vary as measured at different locations. *Materials and Methods:* The objective of this study was to evaluate the differences between the indices of the AU, measured at the handle-free cord (AL) and paravesical (PV), and estimate the degree of agreement and correlation of the same. *Results:* The pulsatility index (PI) and resistance (IR) were measured AU and AL in 8 PV twin pregnancies without maternal comorbidities at the Torrecardenas Hospital. *Conclusion:* The measurement of IR and IP at different locations in the umbilical artery had significant differences. Although the correlation between the two is good, they do not reflect the consistently higher values cuendo measured at PV. Because of the degree of agreement, both measurements can be considered as equivalent and used interchangeably.

PLACENTA ACCRETA WITH PRENATAL DIAGNOSIS IN TWIN PREGNANCY: WEEK OF PREGNANCY TERMINATION

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Introduction: Placenta accreta is a condition that can compromise maternal life due to massive bleeding and morbidity of the surgery itself. There are still controversies regarding different aspects of management, one of which is the optimum time of termination of pregnancy, which should balance the risk of catastrophic hemorrhage with prematurity. Some groups suggest 34 weeks, while others suggest 36 weeks, or 37–38 weeks. *Materials and Methods:* We describe a case of twin pregnancy and placenta accreta. *Results:* Our patient was diagnosed at 19 weeks of gestation with placenta accreta, dichorionic diamniotic gestation, both male fetuses. Control of normal pregnancy every 2 weeks until completion at 37 weeks gestation by elective cesarean.The most common reason for cesarean fits to moderate episodes of metrorrhagia. *Conclusion:* It seems unnecessary to apply a systematic pattern of early termination of pregnancy (e.g., 34 weeks), with attendant risks of prematurity to prevent catastrophic bleeding episodes. Planning for cesarean around 36–37 weeks in asymptomatic patients appears to be a safe strategy.

TWIN PREGNANCY PLACENTA ACCRETA MONOCHORIONIC DIAMNIOTIC IN THE FIRST TRIMESTER

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Introduction: In recent years the frequency of placenta accreta has increased more than 8 times the increase in the cesarean rate. Complications from abnormal placental implantation during the 1st trimester of pregnancy are rare. These conditions are usually detected during the 2nd or 3rd trimester. *Materials and Methods:* We report a case of placental implantation abnormality in the first trimester. *Results:* The patient, aged 31, pregnant at 12 weeks gestation with monochorionic diamniotic login for heavy bleeding and diagnosis of abortion in progress. A vaginal ultrasound scan was performed and a diagnosis made of suspected placenta accreta. After the realization of endocavitario, curettage bleeding ceased. *Conclusion:* The presentation of this case leads us to include in the differential diagnosis of bleeding the first trimester to abnormalities of placental implantation, especially in patients with persistent menorrhagia and risk factors for developing this disease.

OVARIAN CANCER IN TWIN PREGNANCY

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Introduction: The association between cancer and pregnancy is infrequent, with an incidence of 0.02 to 0.1%; ovarian cancer occupies third place among the most common gynaecological malignancies associated with pregnancy, with rates between 1/10,000 to 1/100,000 pregnancies. *Materials and Methods:* To disseminate clinical case of interest to the medical community. *Results:* A 30-year-old pregnant woman with a twin pregnancy of 35 weeks, who consulted for abdominal pain, and increased abdominal girth. Transabdominal ultrasound confirmed space occupying lesion in the right lower quadrant and flank multilobed of 16.3 × 8.9 × 14.7 cm, with concordance in MRI, which is seen as a mixed ovarian tumor. A cesarean was conducted, and the frozen biopsy was diagnosed as ovarian germ cell tumour. Complete surgery was performed, with withdrawal in good condition and currently under chemotherapy regimen. *Conclusion:* The coincidence of occupying ovarian cancer during pregnancy is rare, the dysgerminoma are the most frequently diagnosed malignancy.

SEASONALITY IN TWIN BIRTH RATES, GREECE, 2004–2008

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Introduction: A variety of environmental factors are known to influence pregnancy and birth. It is believed that seasonal variation of polyzygotic maternities is due to seasonal variation in the rates of multiple ovulations rather than to seasonal variation in any of the other reproductive parameters that could, in principle, be responsible (coital rate, spontaneous abortion, probability of fertilization). It is possible that such an hypothesized variation is due to seasonal variation in food consumption. The present study has been

made of seasonality in twin birth rate in Greece between 2004 and 2008. *Materials and Methods:* To test the possible seasonality of ovulation of Greek mothers, we studied all multiple births in all deliveries that took place at the General District Hospital Athens 'Alexandra' during from January 2004 to December 2008. For each delivery, based on the date of birth as well as the duration of pregnancy, we calculated the date of apprehension. Statistical analysis for twins' seasonality was done using a harmonic sinusoidal model. *Results:* During the study period noted there were 569 multiple births from 23,591 deliveries. In the multiple births, 27 (4.8%) were triple pregnancies and 542 (95.3%) were double pregnancies. The 5-year frequency of twinning rate was 2.3%, with the highest rate shown in 2008 (2.9%) and the lowest in 2007 (1.6%). The in vitro fertilization (IVF) pregnancies were 142 out of 569 multiple pregnancies (25%), while the remaining 427 pregnancies (75%) were from natural conception. Statistical analysis provided no evidence for seasonality. However, concerning the natural conceptions, sequential polynomial analysis disclosed a significant fit to a fifth order polynomial curve, with peaks in twins' conception in the fourth trimester as well as in the first trimester. In more detail, the higher peak matches the period of November–December and the lower peak matches to March. *Conclusion:* Our results reveal a preference of twinning conception in particular months, November, December and March. This shows a possible environmental influence on twinning. A longer study period may be provide more evidence for twinning seasonality.

BLOOD PRESSURE IN TWINS WITH AND WITHOUT TWIN-TWIN TRASFUSION SYNDROME

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Introduction: Twin-Twin Transfusion Syndrome (TTTS) complicates 10–15% of monochorionic diamniotic pregnancies and carries a high rate of morbidities and mortality. In addition to unbalanced flow through placental anastomoses, evidence suggests that transfer of circulating vasoactive elements from the donor to the recipient contributes to the pathological process of TTTS. The objective of this study was to test the hypothesis that TTTS recipients have higher blood pressure (BP) at birth than donors, independently from gestational age (GA). *Materials and Methods:* Retrospective evaluation of clinical data was conducted of all TTTS infants born from January 2012 to April 2014 with both twins alive for at least 24 hours (8 pairs; average GA 32 weeks) in comparison with those without TTTS (146 pairs; GA 35 + 4 weeks). Paired analysis of non-invasive BP measurements (BPs) in the immediate postnatal period (first evaluation after birth) and at 24 hours of life. *Results:* In TTTS twins, both systolic and diastolic neonatal BPs at birth were significantly higher in recipients. When expressed relative to predicted BP for gestational age, BPs were lower than expected in donors and higher in recipients. *Conclusion:* Studies of newborn BP report a constant and substained rise in BP values over the first hours to days after birth for all infants, preterm or term, singletons or twins. In contrast, our data indicated a decrease in BP during the first 24 hours of life in TTTS recipients. Moreover, TTTS recipients have significantly higher BP than donors and than BP expected for GA. These elements support a role of molecules, such as angiotensin II, in the pathophysiology of the cardiovascular manifestation of the TTTS. The long-term impact of these early hemodynamic perturbations remains to be determined.

IDENTIFICATION OF AN ADIPOSE SPECIFIC GENE ENVIRONMENT INTERACTION ASSOCIATED WITH BMI

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Introduction: Obesity is a worldwide epidemic that is robustly associated with many comorbidities, including cardiovascular disease and type II diabetes. Recent Mendelian randomization trials have shown obesity to be causal of many comorbid traits, such as LDL cholesterol, blood pressure and insulin sensitivity. Genome-wide association studies (GWAS) have identified hundreds of variants associated with complex disease, many of which are in non-genic regions of the genome. Studies have shown that genome-wide associations are enriched for eQTLs, demonstrating the importance of regulatory variation in complex disease. Comorbid traits such as insulin resistance are thought to act locally in peripheral tissues. Peripheral tissues are therefore interesting targets to interrogate how obesity modifies comorbid associations via gene by environment interactions. *Materials and Methods:* Using RNA-sequencing data from three primary tissues (Adipose, Skin and Blood) and one cell line (LCLs) from 853 deeply-phenotyped healthy twins, we have characterized the interplay between Body Mass Index (BMI), genotype and gene expression in multiple tissues. *Results:* In adipose tissue, 88% of expressed genes are associated to BMI at a 5% False Discovery Rate (FDR) and 50% have an identified cis-eQTL. We identify a novel, genome-wide significant, tissue-specific SNP-BMI interaction on HACL1 expression in adipose tissue, in which HACL1 is over-expressed specifically in obese individuals carrying the C allele of rs1464171. HACL1 catabolizes an insulin sensitizer, which activates PPAR-alpha and Retinoid X receptors, two common type II diabetes drug targets. *Conclusion:* We hypothesize that the genotype-dependent up-regulation of HACL1 in obese individuals could contribute to the comorbidity of insulin resistance.

IS POST-TRAUMATIC STRESS DISORDER (PTSD) ASSOCIATED WITH INCREASED BODY MASS INDEX?

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Introduction: Numerous factors, including diet, activity levels, and genetics, are associated with weight gain in adults. Little research has examined the influence of mental health on weight and no study has examined the association of PTSD and weight in a genetically informative sample. The aim of this study was to assess the association of PTSD symptoms with body mass index (BMI) among members of the Vietnam Era Twin (VET) Registry. *Materials and Methods:*

The VET Registry is a national sample of U.S. male twins born between 1939–1956 and who served on active duty during the Vietnam era (1964–1975). In 1985, 10,738 twins completed a mail survey on health and wellbeing; in 2011, 7,384 twins participated in a similar follow-up survey. In total, 5,513 twins responded to both surveys and had valid measures for PTSD and BMI, including 1,565 complete pairs. PTSD symptoms were assessed in both 1985 and 2011 using the same 15-item symptom scale. The scale items were selected based on *Diagnosis and Statistical Manual* criteria and ranged from 15 to 75. BMI was obtained from self-report of height and weight in 1985 and 2011. Measured BMI from the time of military enlistment was also available. Initial analysis examined the cross-sectional association between PTSD symptom scores, grouped into approximate tertiles, and BMI in 1985 (baseline) and 2011. Longitudinal analysis examined the association between baseline PTSD scores and subsequent change in BMI from 1985 to 2011. Analysis was first conducted on twins as individuals and then the within-pair association of PTSD and BMI was examined. Further adjustment included BMI measured at the time of military enlistment and stratification by zygosity. *Results:* There was little difference in the mean BMI across tertiles of the PTSD scale at baseline in 1985; the mean BMI in the lowest tertile was 25.5 compared with 25.4 in the highest tertile ($p = .62$). However, in 2011 the mean difference comparing the highest and lowest PTSD symptoms tertile was significant (29.3 vs. 28.2; $p < .001$). Longitudinal analysis showed that there was a significant association between baseline PTSD score and change in BMI from 1985 to 2011 ($p < .001$). Those in the highest PTSD tertile gained a mean of 3.5 BMI units compared to a gain of 2.9 BMI units among those in the lowest PTSD tertile. PTSD-associated differences in BMI were no longer statistically significant in the longitudinal within-pair analysis ($p = .19$). Adjustment for BMI at the time of enlistment did not alter these results. *Conclusion:* PTSD is associated with increases in weight among Veterans but this association is in part explained by familial factors. Clinicians should be made aware of the obesiogenic potential of PTSD and treatment programs for PTSD should include weight gain as an outcome.

CLINICAL CHARACTERISTICS ASSOCIATED WITH THE PLANNED AND ACTUAL MODE OF DELIVERY OF TWINS: AN ANALYSIS OF 22,864 TWIN PAIRS FROM 32–41 WEEKS

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Introduction: A planned vaginal delivery (VD) for twins may result in a vaginal delivery, an intrapartum cesarian section (CS) for both children or in a combined delivery. The latter is associated with the highest neonatal and maternal morbidity. We aimed to identify maternal, pregnancy, fetal, and hospital-related indicators associated with the planned and actual mode of delivery for twins. *Materials and Methods:* We included all twin pregnancies in The Netherlands Perinatal Registry (PRN) with a GA of 32 + 0 – 41 + 0 weeks from 1–1, 2000 – 1-1, 2008. We excluded incomplete data sets, twins < 500 grams, twins with lethal congenital anomalies, and pregnancies with a fetal demise before delivery. Women who delivered by primary CS were included in the planned CS group; and those who delivered both twins vaginally or one or both twins by intrapartum CS in the planned VD group. Univariable and multiple logistic regression analyses were performed to identify indicators associated with planned CS; the same analyses were done for the planned VD group to identify indicators associated with intrapartum CS. *Results:* Of 22,864 women; 4,359 (19.1%) delivered by planned CS and 18,505 (80.9%) by planned VD. Of these, 14,116 (76.3%) delivered vaginally, 3,562 (19.3%) per intrapartum CS and 827 (4.5%) via combined delivery. Maternal age (31–40 years (OR 1.27; ≥ 41 years, 2.98), parity (nulliparity, OR 1.49; primiparity, OR 1.20), previous CS (OR 3.67), pre-eclampsia (OR 2.11), fetal position (cephalic-noncephalic, OR 1.82; noncephalic-cephalic, OR 21.10; noncephalic-noncephalic, OR 24.71); weight discordance (child B vs. child A ≤ 80%, OR 1.75), small for gestational age (both twins < p10, OR 1.15; twin A < p10, OR 1.21; twin B < p10, OR 1.23), and type of hospital (university, OR 1.36) were significantly associated with a planned CS. Gestational age (32 + 0 - 32 + 6, OR 0.74; 33 + 0 - 33 + 6, OR 0.65; 34 + 0 - 34 + 6, OR 0.64; 35 + 0 - 35 + 6, OR 0.64; 36 + 0 - 36 + 6, OR 0.70; 39 + 0 - 39 + 6, OR 0.38; 40 + 0 - 40 + 6, OR 0.20), and annual twin deliveries per hospital (75–100, OR 0.75) were significantly associated with planned VD. Maternal age (31–40 years, OR 1.30; ≥ 41 years, 2.54), parity (nulliparity, OR 4.21; primiparity OR 1.36), previous CS (OR 7.03), pre-eclampsia (OR 1.35), gestational age (38 + 0 - 38 + 6, OR 1.16; 39 + 0 - 39 + 6, OR 1.44; 40 + 0 - 40 + 6, OR 1.75), fetal position (cephalic-noncephalic, OR 2.27; noncephalic-cephalic, OR 13.63; noncephalic-noncephalic, OR 21.92); weight discordance (child B vs. child A ≥ 125%, OR 1.45), type of hospital (university, OR 1.36; non-university teaching, OR 1.11), and little annual twin deliveries per hospital (0–24, aOR 1.16) were significantly associated with delivery by intrapartum CS after planned VD. Only gestational age (32 + 0 - 32 + 6, OR 0.75; 33 + 0 - 33 + 6, OR 0.74; 34 + 0 - 34 + 6, OR 0.72; 35 + 0 - 35 + 6, OR 0.74; 36 + 0 - 36 + 6, OR 0.85), small for gestational age (twin A < p10, OR 0.78), and higher annual twin deliveries per hospital (50-74, OR 0.81; 75-100, OR 0.70; ≥ 100, OR 0.62) were significantly associated with a successful VD for both twins. *Conclusion:* We found a strong association between non-cephalic fetal position of the first child and a previous CS for a planned and actual delivery via CS. Nulliparity was associated with a greater chance on an intrapartum CS.

PATHOLOGY OF CO-TWINS WITH 'VANISHED TWINS' IN HIGH RISK PREGNANCY

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Introduction: Early embryo loss is most common pathology in dichorionic diamniotic (DCDA) twins during the first trimester of pregnancy. The exact causes of 'vanishing twins' are hard to establish, but considered the same as causes of early pregnancy loss in singletons: aneuploidies, infection, hormonal pathology, failed implantation/placentation and others. A higher rate of obstetric complications were shown in IVF patients with 'vanishing twins', but no additional risk for the other co-twin was proved. The purpose of this study was to analyze the spectrum and rate of co-twins pathology in cases of first trimester of embryo loss among spontaneous and ART DCDA pregnancies. *Materials and Methods:* Data from medical records of 178 high risk pregnant women with DCDA twin gestations were analyzed. Among them, 132 (74.2%) had spontaneous gestations and 46 (25.8%) had ART gestations. There were 37 (28%) patients with 1st trimester one embryo loss in the spontaneous gestation group and 7 (15.2%) in the ART group ($p < .05$). For subsequent analysis, records of patients who have returned for further following up were selected: 6 in the 'vanished twin' ART group and 27 in the spontaneous gestations 'vanished twin' group. For the comparison group, DCDA patients with no embryo loss in the 1st trimester of pregnancy and uneventful development of at least one co-twin were selected: 33 ART and 79 spontaneous gestations. The rate of fetal structural malformations (SM), intrauterine growth restriction (IUGR) and fetal death was calculated. *Results:* Among

ART patients, SM of co-twin were diagnosed in 2 cases in the 'vanished twin' group and in 3 cases in the comparison group, which amounted to 33.3% and 9.1% respectively ($p > .05$). There were 2 (6.1%) cases of fetal death and 5 (15.2%) cases of selective IUGR in the comparison group, but none of these complications were registered in the 'vanished twin' group. In patients with spontaneous gestation, SM of a co-twin were diagnosed in 4 cases of the 'vanished twin' group and in 31 cases of the comparison group – 14.8% and 39.2% respectively ($p < .01$). The rate of fetal death amounted to 7.4% in the 'vanished twin' group (2 cases) and to 5.1 % in the comparison group (4 cases). IUGR was found in no patients with a 'vanished twin' and in 6 patients of the comparison group (7.6%). *Conclusion:* In high risk pregnant women with spontaneous DCDA twins after 1st trimester loss of one embryo, there is a decreased risk of SM of the other co-twin. So, the realization of severe threat for current pregnancy through the death of one embryo possibly takes the other co-twin out of high risk.

LONGEVITY STUDY ON TWINS INDICATES "INDIVIDUAL GENOME LOCK-UP" OF GENES

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Introduction: The inheritance of longevity has been known in Indian literature since 4000 BCE. A large number of epics have been known for centuries in the world literature, but scientific studies aiming to understand the longevity inheritance only started at the beginning of 20th century. Most animals are now known to correspond to a more or less fixed variable of lifespan; experimental studies with Drosophila and other organisms have confirmed the existence and transmission of genes for longevity. *Materials and Methods:* Epidemiological studies on human twins with significant concordant life span records from a series of monozygotic twins compelled Luigi Gedda and his associates to propound the 'Ergon-chronon system', which means that each gene has a fixed energy and time to act and thereafter exhausts its activity within individuals. This was an extra dimension to Haldane's concept of 'time and place' for gene action, accepted universally for gene action, but that does not indicate any exhaustion. In our studies, pedigrees for studying longevity of twins (8 MZ and 15 DZ twin pairs) and non-twin families (22 families – three generation records noted from relatives and family elders) have indicated the following basic inferences. *Results:* The life span of individuals may be controlled by polygenic inheritance. (1) The same genes for the same function are locked in a different mode among different individuals in a different family track; this 'Individual Genome Lock-up' runs in families, as indirectly revealed by twin studies. (2) The genes for longevity express and pass on the Mendelian path but can always be suppressed by somatic mutations in one cotwin. (3) Given everything proceeds normally, the longevity passes on, but, genetic disorders and mutations such as cancers may derail the normal process. (4) Accidents, wars and aggressive social turmoil may eradicate all other situations. *Conclusion:* So, it may be that humans have longevity genes with a maximum 'time set up', but each individual has their own 'genomic lock-up' that finally influences turning off, under all other normal situations.

DIZYGOTIC TWINNING IS RELATED TO GENETIC LOAD AND FRATERNAL COMPONENT

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Introduction: Extensive studies on birth statistics (more than 18 million) covering the period from 1960–2000 from various parts of Central India have categorically suggested that this multifactorial information gathered can help in monitoring human health welfare in a society. Birth statistics include number of male and female births, sex ratio, congenital malformations, twin and multiple births (same and different sex combinations) and several unusual situations. *Materials and Methods:* Comparative frequency estimates of each event indicate definite interaction of parental genetic transmission and induced environmental stresses. Genetic loads (including chromosomal load) variably depend on heredity as well as changing food and excessive drug usage (drug abuse?) habits over past few decades. Goswami (1987) had hypothesized that a rise in a population depends on fecundity of females and fertile males, their inbreeding status and their age dependent physiological problems, which influence mean live births. The formula developed was Fraternal component = Mb x G/ (F xSa) Sr (Mb = mean birth rate; G = growth percentage; F = inbreeding coefficient ; Sa = still births + abortions and Sr = sex ratio). *Results:* A great coincidence was found in that the designated fraternal component almost equals the dizygotic twinning rate of the population in question. Therefore, the meticulous maintenance of birth statistics in a population, with records of malformations and other congenital traits, can help in assessing increasing environmental and genetic hazards within a population. Increasing twinning rates — particularly dizygotic rates — have been reported to be indirectly correlated to increasing external environmental influences associated with extra consumption of drugs/ chemical combinations and also with imposed migrations. *Conclusion:* The frequency of twinning estimates has become insignificant these days but I suggest that this should go on at the population level as the data can indicate environmental mutagenesis and silent genetic deaths in human populatio(s).

SLEEP BEHAVIOR IN TWINS FROM INFANCY TO ADULTHOOD

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Aim and Research Questions: Sleep behavior over time usually reflects both individual differences in children and environmental factors. In the present study this is explored in a group of twins followed from infancy to adulthood. Are genetic factors most likely to explain differences in sleep patterns in MZ and DZ twin pairs? *Sample and Method:* The sleep behaviors of a Norwegian sample of 40 pairs (28 MZ and 12 DZ) of same-sexed twins, were assessed at 9 months, 6 years, 15 years, and 30 years of age. The methods used were interviews with mothers (at 9 months and 6 years) and self-reports (at 15 and 30 years). The sleep measures included hours of nightly sleep, regular bedtime, morning awakening, sleep onset time, and frequency of night wakings. At 15 years, only data on frequency of night wakings were available. *Data Analysis:* The sleep behavioral measures were the same at all measuring points. The analysis at each age is within-pair correlation. *Results:* No consistent patterns across age was found for any of the sleep measures. In infancy and at 6 years of age there was a striking similarity both in MZ and DZ twin pairs concerning sleep behavior under mother's control, such as bedtime and morning wake-up time. However, sleep onset and number of night wakings were significantly more similar in MZ twins than in DZ twin pairs. *Conclusion:* At later ages, a genetic influence on sleep behavior may explain the stronger similarity found within MZ twin pairs concerning regularity and sleep onset time.

DEMISE OF THE LEADING TWIN IS AN INDEPENDENT RISK FACTOR FOR EARLY PRETERM BIRTH

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Introduction: This study is aimed to investigate the effect of fetal demise on pregnancy outcome, and to address the question whether the order of the dead fetus has clinical importance. *Materials and Methods:* This population-based retrospective cohort study included all twin deliveries at our medical center during the years 1988–2013 ($n = 9{,}992$ neonates). Overall, 81 pairs of twins (162 neonates) had a fetal demise of a single fetus. The remaining cases (9,730 neonates) were twin deliveries of two live-born neonates who served as a comparison group. In the second stage of the analysis, we compared pregnancy outcome according to the demise of the leading or the second twin. *Results:* The rate of stillbirth of one twin was 1.63% (162/9892). Twin gestations with stillbirth of one twin had a higher rate of APGR score >of 8 at 1st and 5th minutes and SGA neonates ($p < .001$ for both), and a lower rate of non-vertex presentation of the second twin ($p = .018$). Mean gestational age at delivery was lower in those with stillbirth of one twin than in those with two twins alive ($p < .001$). In the fetal demise group 29% (47/162) were the leading twins and 71% (115/162) were the second twin. The mean birthweight of those who had fetal demise of the leading twin was lower than that of those with fetal demise of the second twin ($p = .017$) and they had a higher rate of oligohydramnios ($p = .042$). Women with fetal demise of the leading twin delivered earlier than those with fetal demise of the second twin(fetal death of the leading twin 31.5 ± 3.49 vs. fetal death of the second twin 34.49 ± 3.54, $p < .001$). Neonatal mortality did not differ among the groups. Among women with demise of one of the twins, preterm delivery was more prevalent in those who had a demise of the leading twin 95.8% (23\24) than those who had a demise of the second twin66,7% (38\57), ($p = .005$. Moreover, after adjustment for maternal age and history of prior preterm birth, the demise of the leading twin was an independent risk factor for early preterm birth before 34 weeks of gestation. (adj. OR 3.985; 95% CI 1,946–8.163, $p < .001$). *Conclusion:* In cases of single fetal demise in twin gestation, the death of the leading twin is an independent risk factor for early preterm birth.

GENOMIC LITERACY OF TWINS AND THEIR FAMILY MEMBERS

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Introduction: Genomic literacy refers to the ability to fully understand and use information regarding the genome. Literacy is the ability to read and write; however, the term has recently been extended to a wide range of areas. For example, health literacy involves not only the ability to read and write but also the ability to understand and use information regarding health. The objective of the present study was to elucidate the relationship between genomic literacy and health literacy as well as the relationship of these two abilities with disease prevention and health promotion. *Materials and Methods:* We requested the cooperation of several associations; for example, we invited parents of twins and conducted interview surveys. The Osaka City University has approved the ethical review of this research. Recorded interviews were sequentially transcribed to accumulate data, and a grounded theory approach was used to perform the analysis. Thus far, we have interviewed five members of two families: two fathers, one mother, one older brother of twins, and one twin. To avoid missing potentially important categories, subjects were randomly selected (open sampling). *Results:* We focused on analyzing those experiences that we considered important for genomes, according to the information on nurture of identical twins. The result showed that subjects tended to regard genomes as individual dimensions. In other words, they individually assessed their experience on the basis of their personal interpretation. Furthermore, subjects interpreted events as personal dimensions of individuals and did not recognize genomes as collective dimensions with familial or regional characteristics. Subjects did not share common perceptions with their family members, and thus showed different views on the same event, which may have been because of having fewer opportunities to share ideas about genomes with them. *Conclusion:* We intend to conduct further interviews to understand how to extend family members' interpretation of genomes from 'personal dimensions' to 'collective dimensions' — familial or regional characteristics —and how to share personal experiences between family members for disease prevention or health promotion.

TWINSHIP AS A RESOURCE

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Introduction: Aiming to perform the first sociological survey of Hungarian twins, our main question was whether being a twin has positive consequences on one's life. Adult twins completed our questionnaire at three Hungarian summer twin festivals, in hospitals during medical twin studies, and on some websites online. Data represented 140 twin pairs(mean age:38.2 ± 14.6 years). We employed some indices for measuring the resource nature of twinship. Three main types of benefits were distinguished: profit of attraction, as a sort of 'material capital'; the easier obtainability of cultural goods when twins take part in it, as 'cultural capital'; and positive aspects of an a priori existing dyadic relation, as 'relational capital'. We were interested in the difference among types of twins regarding advantages. We paid special attention to the five groups of twins, derived from gender and zygosity (i.e., MZ females, MZ males, DZ females, DZ males, opposite-sex pairs). *Materials and Methods:* In our study, we employed some indices for measuring the resource nature of twinship. We defined the range of benefits related to twinship more broadly than educational achievement and social status. Our questions encompassed the benefits of social relations, twin appearance and the opportunity of being mistaken, and the feelings about and evaluation of these facts. Three main types of benefits were distinguished: profit of attraction, as 'material capital'; the easier obtainability of cultural goods when twins take part in it, as a sort of 'cultural capital'; and positive aspects of an a priori existing dyadic relation, as 'relational capital'. *Results:* The role of gender: (1) About the gender distribution of variables forming the index of the general experience of twinship, a significant effect was found on the subjective importance of twinship. (2) No major difference was observed between male and female respondents with regard to the benefit caused by their physical abilities (attraction, or 'material capital'). (3) When evaluating the indices constructed for active and passive uses of twinship, a significant result is that women report more actively using their twinship status than men. Differences among twin types: (1) Mono- or dizygotic: MZ twins had significantly higher values in all fields, meaning that twinship was much more important for them, and they took greater advantage of the possibilities given by twinship, both in an active and a

passive way. (2) Differences among the five twin types: the ranking of scores is as follows: MZ women, MZ men, DZ opposite-gender, DZ women, and DZ men. *Conclusion:* Our research showed that Hungarian twins involved in our research basically enjoy their twinship; during their lives they used and still make use of the different benefits given by it. Dividing the sample population by gender and zygosity reveals a heterogeneous picture. Of note, female responders, especially identical twins, exploited the capital of being a twin in a greater proportion than other groups. We investigated only one side of the resource dilution or strengthening theory, that of the strengthening; and according to our results a twinship is beneficial for twins, with benefits varying in magnitude from one twin group to another. Our findings reinforce two points: First, it is problematic to speak about twins on a general level, because MZ and DZ twins are very different in several ways. Second, it is important to make additional distinctions than merely zygosity, as in reality there are five types of twins, and their possibilities and behavior is also very diverse.

TWIN ZYGOSITY ANALYSIS COMPARING FACIAL 3D-STEREOPHOTOGRAMMETRY AND DNA METHOD

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Introduction: The aim of this study was to compare 3D facial stereophotogrammetric method versus DNA method in twin zygosity determinations. *Materials and Methods:* The faces of 105 pairs of young adult Lithuanian twins were photographed with stereophotogrammetric device (3dMD Atlanta, Georgia) and blinded zygosity was determined according to similarity of facial form, calculated from linear distances. *Results:* The results showed that zygosity determinations were in 75% to 89% of cases similar compared to DNA-based results. The results varied according to 81 different classification scenarios in 3D, including 3 groups, 3 features, 3 different scaling methods and 3 threshold levels. It appeared that coincidence with 0.5 mm tolerance was the most suitable feature for classification, and relatively reliable zygosity recognition is possible even with a quite simple classifier. Also, leaving out scaling improves results in most cases. Scaling was expected to equalize the magnitude of differences and therefore lead to better recognition performance. Male pair zygosity recognition in 3D was on a higher level (88%) compared with females (86%). Knowing the DNA test MZ/DZ ratio before 3D analysis did not have any considerable effect in the results. *Conclusion:* The faces of young dizygotic twins may appear so similar that it is very hard to define a feature, that would help classifying the pair as dizygotic, suggesting that age also should be considered. Correspondingly, monozygotic twins may have faces that are spatially and formally quite different. Such deviant twin pairs are interesting exceptions but they form a considerable portion in both zygosity groups, and may violate heritability calculations.

FAMILY CARE NURSING IN THE MULITPLE BIRTH FAMILIES – EVIDENCE-BASED STRENGTHENING IS NEEDED

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Introduction: In recent years the research interest in multiple birth families (two or more children born at the same time) has focused on the pregnancy and babies' health, and the relationship between the mother and her child and the twin-twin relationship, but little interest has been addressed to parenthood and daily life. There has not been much attention focused on family care nursing in the different context of health care and homes. The lack of knowledge has been noticed by parents and professionals. *Participants and Methods:* This research describes everyday life and family care nursing in twin families from the point of view of parents, public health nurses, and family care workers. The material consisted of interviews with the participants ($n = 38$), written output, and the researcher's notes, which has been analyzed by van Manen's method — the description of the phenomenon through the concept of a lifeworld. *Results:* The phenomena of the lifeworld of multiple birth families consists of three essential themes: 'a state of constant vigilance', 'ensuring that they can continue to cope' and 'opportunities to share with other people'. The parents would have wanted more information about the life in multiple families, pregnancy and childbirth, feeding, supporting the growth and development of twins. The public health nurses recognized the strain on the parents, and supported their parenthood. However, any special information the parents received was restricted to supporting the twins' individuality. For family workers, aiding parents' everyday management meant strengthening their parenthood by supporting and guiding their everyday life and giving parents moments of rest. The security brought by family care workers meant facilitating daily life, achieving trust, and sharing responsibility in the care for all children and home.

Conclusion: (1) Being a parent in multiple families is different from being a parent for just one child. (2) The social worker and health professional need further tools and training to be able to empower parents of twins. It means listening to parents to get a deeper understanding their situation. Special information is needed on how to target guidance that meets the needs of family. (3) Education and research are needed to provide evidence-based family care nursing in a different context. (4) Evidence-based family care nursing requires cooperation between nurses and family care workers, by developing a model and an indicator for family care work in multiple birth families. This will be a challenge for future research.

REDUCTION AS A METHOD TO DESCRIBE THE LIFEWORLD OF THE MULITPLE BIRTH FAMILIES IN FINLAND

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Introduction: The aim of this presentation is to describe reduction as a method using van Manen's phenomenological-hermeneutic research approach and provide an empirical example regarding multiple-birth families' lifeworld in Finland. *Participants and Methods:* The research describes reduction as a method in the research process. The material consisted of interviews with parents of twins, public health nurses and family care workers ($N = 38$), written outputs, and the researcher's notes. The material has been analyzed by van Manen's method, which is the phenomenon of the concept of a lifeworld with modalities of time, body, relation and space. *Results:* Reduction as a method gives the opportunity to deeply understand the lifeworld of multiple families. Reduction in van Manen's method distinguishes the methodological usefulness of heurism(wonder), ontology (holistic understanding, concept of lifeworld), concreteness (literature, experiences), eidetic (natural attitude, lived experiences), hermeneutics (preunderstanding, hermeneutic circle) and methodology. In the research process, reduction helps to keep research stages separate, but also as a whole. The phenomena of the lifeworld of multiple birth families consists of three themes: 'a state

of constant vigilance', 'ensuring that they can continue to cope' and 'opportunities to share with other people'. The social worker and health professional need to listen to parents to more deeply understand their situation, and need further tools and training to be able to empower parents of twins. *Conclusion:* (1) Reduction as a method provides the opportunity to more deeply understand the life-world of multiple families. The social worker and health professional need further tools and training to be able to empower parents of twins. Accommodating the distinctive need for support in multiple-birth families should develop education. (2) Evidence-based family care nursing is needed for professionals working with multiple-birth families in different contexts (e.g., hospital, public health, homes). (3) Propositions for further development are connected to support and receiving information regarding multiple-families. Developing a model and an indicator for family care work in multiple-birth families will be a challenge for future research.

CONGENITAL HEART DEFECTS IN TWINS: OCCURRENCE AND PROGNOSIS

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Introduction: We have recently shown that congenital heart defects (CHD) are more frequent in both MZ and DZ twins than in singletons (Herskind et al., Circulation 2013). The excess risk was also found for non-prematurity related defects and operated CHD. Here we assess the prognosis for CHD in twins, comparing hospitalizations and mortality for CHD twins with those for non-CHD co-twins, non-CHD twins generally, and CHD singletons. *Materials and Methods:* We investigated CHD occurrence and prognosis in all twins and 5% of all singletons born in Denmark in 1977–2009 and followed through 2013 by linking the Danish Twin Registry and Statistics Denmark registers. *Results:* Among 63,459 live-born twin individuals, a total of 1,100 twins (1.73%) had a CHD registered in the Danish National Patient Register, whereas the corresponding numbers for singletons were 937 of 99,337 (0.94%), that is, an 85% (95% CI: 70–102%) increased risk for CHD in twins. A total of 907 twin pairs were discordant for CHD. During the follow-up, 8.6% (94) CHD twins died compared to 11.0% (103) CHD singletons. Of these, 55.3% of CHD twins (52) and 71.8% of CHD singletons (74) died after the neonatal period (0–28 days). Logistic regression analyses adjusted for sex, birth cohort, and twin dependence revealed that, in the first 28 days of life, CHD twins had significantly higher mortality than non-CHD twins generally (OR = 2.1, 95% CI [1.5–2.8]), though not compared to non-CHD co-twins (OR = 1.3, 95% CI [0.8–2.2]). Despite a 5.1 times higher proportion of prematurity (61.9% vs. 12.1%, $p < .001$), CHD twins had only moderately increased neonatal mortality compared to CHD singletons (OR = 1.6, 95% CI [0.97–2.6]). Cox regression analyses adjusted for sex, birth cohort, and twin dependence revealed that after the neonatal period, CHD twins had markedly higher mortality than non-CHD co-twins (HR = 5.5, 95% CI [2.7–11.3]) and non-CHD twins generally (HR = 9.0, 95% CI = [6.7–12.1]), but there was a tendency towards lower mortality for CHD twins compared to CHD singletons (HR = 0.8, 95% CI [0.6–1.2]). A similar tendency after age 1 year was seen for hospitalizations. *Conclusion:* Hospitalization pattern and mortality in up to 36 years of follow-up indicated a better prognosis for CHD twins compared to CHD singletons after the neonatal period. A likely mechanism is selective intrauterine and neonatal mortality of twins with severe CHD.

GREATER RESEMBLANCE OF TELOMERE LENGTH IN DIZYGOTIC TWINS WITH INCREASING PATERNAL AGE

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Introduction: Leukocyte telomere length (LTL) is a complex human trait. It is longer in women than men and influenced by environmental factors. LTL is longer in offspring of older fathers, a finding that might stem from the longer telomeres in sperm of older men. *Materials and Methods:* The analysis is based on two independent twin studies, comprising 939 twin pairs, The discovery sample comprised 137 dizygotic and 167 monozygotic Danish twin pairs (both men and women) and the replicative sample comprised 217 dizygotic and 368 monozygotic British twin pairs (all women). For the statistical analysis, generalized additive mixed models and the polygenetic biometrical model were fitted. *Results:* An increase in the resemblance of LTL between dizygotic twins of older fathers could be shown, which is not the case for monozygotic twins. The biometric model attributed the increased resemblance in LTL in the dizygotic twins to shared environment factors. *Conclusion:* We hypothesize that this phenomenon results from a paternal age-dependent germ stem cell selection process, whereby the selected stem cells are longer, more homogenous with respect to telomere length and share resistance to aging.

A BAYESIAN APPROACH TO MIXTURE DISTRIBUTIONS OF TWIN DATA WITH AN APPLICATION TO CORTISOL AWAKENING RESPONSE (CAR)

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Introduction: The estimation of regression models is sometimes impeded by data that are not amenable to conventional univariate distribution models. Mixture distributions address the case where the underlying population is composed by a number of subpopulations that are not characterized by any observed variable or biomarker. The mixture approach may in particular be relevant where clinical, or other considerations, suspect latent variables to form groups of subpopulations. Such models are well known in 'classical statistics', but have not been explored in the context of twin data and the concept of heritability. *Materials and Methods:* We use a two-component mixture model approach to twin data and imposed the conventional ACDE models to each of the two components. For the present study we did, however, only use the ACE variant of the ACDE model. The model was implemented in a Bayesian framework and used OpenBUGS for its estimation. Simulated data were used for demonstration of general properties of the model. For the application we used measurements on cortisol awakening response (CAR) from 748 twin individuals (353 men and 395 women) aged 28–78 years, recruited from the Danish GEMINAKAR cohort, a

longitudinal prospective study on twins initiated in 1997–2000. In particular, it was of interest to consider the change in cortisol level during the first 30 minutes after awakening. It is common practice to distinguish between 'responders' and 'non-responders' for changes in CAR, but these are only differentiated by a somewhat arbitrary threshold value of 2.5. *Results:* We present asymptotic properties of the model, by using simulated data sets of varying sample sizes. These show good asymptotic coverages for the A-, C- and E components of the components for each of the two subpopulations. Preliminary analysis showed that the application of the model to the CAR data allowed for estimation of the mean CAR for 'responders' and 'non-responders', the proportion of 'non-responders' and their separate A-, C- and E- components - analysis is still ongoing. *Conclusion:* We have extended the conventional (univariate) ACDE model to handle data that are a composite of two (or more) subpopulations. Besides characterizing the two subpopulations and their proportions, the model also allows for the estimation of separate heritabilities for the two subpopulations. Neglect of the composite structure of a sample population may lead to erroneous conclusions on all key statistics. The model is essentially nonlinear and we have demonstrated how it can be implemented using OpenBUGS.

AUSTRALIAN TWIN AND FAMILY STUDIES OF MAMMOGRAPHIC DENSITY AND BREAST CANCER: INSIGHTS INTO EARLY-LIFE RISK FACTORS

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Introduction: Twin studies allow insights into early-life risk factors by having twins compare one another for important developmental milestones (such as age, height, weight and breast size at time of puberty). Hamilton and Mack found that differences between twins in their age at puberty in part determine differences in their breast cancer status, and for pairs in which both were affected, differences in age at diagnosis. Within-pair comparisons control for unmeasured risk factors do not give 'biased' estimates; they give unbiased estimates of important parameters not possible using unrelated persons alone, and are especially relevant to epigenetics. *Materials and Methods:* Mammographic density adjusted for age and body mass index predicts breast cancer risk. From studying repeat measures for participants in the Australian Breast Cancer Family Study, we have found that the mammographic density measures that predict disease risk are highly correlated with over time (correlation between two measures 10 years apart $\sim$ 0.9). We have studied the mammographic density measures that predict breast cancer risk for 884 twin pairs from the Australian Mammographic Density Twins and Sisters Study. Twins were asked to respond the same, before, after, or to the questions: (1) 'Did you get your first period before or after your twin?', (2) 'When you got your first period, were taller or shorter than your twin?', (3) 'When you got your first period, were you heavier or lighter than your twin?', and (4) 'Did your breasts develop before or after your twin?'. The percentage of twin pairs who gave responses in perfect agreement with each other was 68%, 77%, 70% and 63% for (1) age when periods start (puberty), (2) height at puberty, (3) weight at puberty, and (4) age when breasts develop, respectively. We are now conducting a study of MZ and DZ female twin pairs in which one or both have had a diagnosis of breast cancer and measure environmental lifestyle factors by questionnaire — including the above within-pair comparisons at the time of puberty — and will measure genome-wide methylation using the Illumina Infinium HumanMethylation450 BeadChip from a blood sample and analyze this using a novel supercomputer-enabled method called DEPTH (DEPendency of associations on the number of Top Hits). Using a within-same-sex twin pair design that controls for age, sex, genes and shared family environment, we will try to identify risk factors for breast cancer using disease discordant pairs, and risk factors for time to diagnosis using disease concordant pairs. *Results:* From the Australian Mammographic Density Twins and Sisters Study we found that the twins who report having the larger breasts at puberty are on average at greater mammographically-predicted risk of breast cancer. Within-pair differences in weight at puberty and age when breast develops predicted within-pair differences in MD ($p = .003$ and .02, respectively). This finding for MD with respect to weight at puberty is consistent with our findings from a prospective study of Tasmanian girls for whom we had heights and weights measured throughout school years in the late 1960s and early 1970s. *Conclusion:* The new project will provide a better understanding of the roles of childhood and adolescence on risk of breast cancer. It will also give a better understanding the role of methylation status on risk of breast cancer. This could lead to identification of a non-invasive biomarker for breast cancer risk that could also predict risk of tumor recurrence and progression. Furthermore, methylation status could be modified by lifestyle exposures, and detection of strong associations between other breast cancer risk factors and methylation status could substantially advance opportunities for prevention. We will describe the study protocol and report on data collection to date, and discuss the potential for this design to be replicated and data pooled across multiple studies using the international network of twin registries.

ICE FALCON: FALSIFYING THE MULTIVARIATE TWIN MODEL

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Introduction: A good statistical model should allow for falsification; that is, make predictions that can be tested. The multivariate twin model assumes that the only causes of cross-trait cross-pair associations are unmeasured familial causes that predispose to multiple traits. It is possible, however, that there are — perhaps in addition — direct causal relationships between traits. *Materials and Methods:* To test this, we have developed a regression approach called Inference about Causation from Examination of FAmiliaL CONfoudning (ICE FALCON). In essence, ICE FALCON asks whether a cross-trait cross-pair association between an outcome Y1 for a given twin and the predictor X2 of their co-twin decreases after adjusting for the predictor X1 of the given twin. Such a finding is consistent with, but of course does not prove, that there is in part a causal relationship between X and Y. This can be viewed as a one-tailed test of a null hypothesis determined by a measured putative cause, just as the classic twin model allows a similar statement to be made about putative unmeasured genetic factors by testing if MZ pair correlations are greater than DZ pair correlations. We can fit models for both continuous and binary outcomes using various statistical packages, including STATA. Inference requires bootstrapping, and this has

been implemented in R. *Results:* In this talk, we will describe applications to: longitudinal tracking in mammographic density; determine the relationships between bone density and bone architecture; address the role of the atopic march in explaining the association of infantile eczema with childhood asthma and hay fever, and how this led to discovering new asthma susceptibility genes; and psychometric traits that have implications for the prevention of anxiety and depression. *Conclusion:* ICE FALCON tests the adequacy of classic twin models and is another approach for using data from twin pairs to give insights not possible from the study of unrelated persons alone.

HERITABILITY OF DISEASE – WHAT IT IS AND WHAT IT ISN'T

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Introduction: In 1918, Ronald Fisher defined heritability — for a measured continuously distributed trait - as the proportion of population variance explained by genetic factors. He showed that the genetic component of variance is transmitted to future generations and thereby related Mendelian inheritance of qualities to genetic variance of quantities. The absolute genetic variance, not a percentage, is what was important. Fisher did not like the way term heritability was being used, referring to its 'hotch-potch of a denominator', and admonished that 'loose phrases about the 'percentage of causation', which obscure the essential distinction between the individual and the population, should be carefully avoided'. *Materials and Methods:* Translating the concept of heritability to binary traits, such as disease status (affected vs. unaffected), has been problematic. One can apply the continuous trait approach to the binary trait but the resulting estimates are typically small and it is virtually never used. Instead, the prevailing paradigm has been to assume an underlying latent (i.e., unmeasured) scale representing risk, often referred to as 'liability', make distributional and modelling assumptions (which are untestable) under which inference is made as if this was a measured continuous variable. When presented, it is often implicitly assumed that 'heritability of liability' is the 'heritability of disease'. Whereas the disease concordance for MZ pairs gives an idea of the maximum variance in liability or risk due to genetic factors, the major issue that has not been specifically addressed is: How can one ever know the total variance? *Results:* For any given observed familial risk (increased risk for relatives of an affected) there are an infinite set of possibilities for: (1) the correlation between relatives in underlying risk; and (2) the gradient of risk across the underlying risk, irrespective of the underlying distribution of underlying risk (see, e.g., 3–5). That is, a given increase in risk for the MZ co-twin of an affected twin is consistent with 100% heritability and one gradient of risk, or any heritability $<100\%$ and a corresponding (smaller) gradient of risk. It all depends on the extent of variation in risk explained by non-familial factors, which likely varies across populations and time, but which can never be known. The all-or-nothing assumption of the standard liability model is arbitrary, and different estimates of correlation in liability arise under other scenarios, such as assuming risk is $<100\%$ for people above a threshold determined by disease prevalence. *Conclusion:* Therefore, estimates of heritability for a disease are virtually meaningless. Further, in popular parlance the expression 'heritability of a disease' conveys a measure of the 'proportion of disease due to genes', which is patently not true, no matter what model has been assumed.

TOWARDS A GLOBAL TWIN REGISTRY USING THE WORLD WIDE WEB

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Introduction: Research involving twins has so many advantages over conventional studies of unrelated persons alone. This is especially important for within-pair epidemiologic, epigenomic and other 'omic studies using pairs discordant for disease or exposure who are matched naturally for major potential confounders. The benefit of these designs is that sampling bias is not an issue, so data from different sources can be pooled. One issue is the availability of sufficient numbers of samples from the existing twin registries, which cover but a fraction of the world's population. *Materials and Methods:* Given the power, penetration and accessibility of the internet, is it realistic to work towards a global twin registry? Twins from anywhere in the world, and irrespective of whether there is a local twin registry, could register their interest in being involved in research and complete an online questionnaire asking about, for example, their disease and exposure statuses. A critical step in launching this would be the involvement of, and promotion by, existing twin registries, which could benefit greatly from the collection of — and of course access to — such data on their membership and the opportunities for recruitment, enhancement and involvement in new studies. *Results:* Twins could also benefit from web-facilitated communication such as social media, with and between twins, which would play an essential role in the recruitment of twins. One model for this is ResearchMatch (www.researchmatch.org), which has the goal of bringing together people (such as those with rare diseases) and trying to find research studies and researchers looking for volunteers to participate in their studies. *Conclusion:* This talk intends to open discussion on the logistical, ethical and other issues involved in this potentially transformative concept that could place twin studies — with their obvious and many advantages over studies of unrelated individuals alone — at the cutting edge of international research.

CHARACTERIZATION OF CHILDHOOD MEDICAL CONDITIONS BY ADULT TWINS

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Introduction: Childhood exposures are increasingly being linked to adult diseases. In case-control studies, the subjects' early childhood health history is poorly assessed by recall. However, identical twins customarily rank themselves with respect to the magnitude or frequency of experience, and these useful rankings can be validated by their mothers. *Methods:* We compared subjective intra-pair rankings of the frequency and magnitude of childhood illnesses, developmental milestones and body size provided by the members of 126 adult identical twin pairs (mean age = 31) to objective person-specific recollections and to responses from their mothers (mean age = 57). *Results:* More informative (i.e., fewer 'don't know' or 'same') responses were obtained from the intra-pair rankings than from comparisons between objective recollections. Agreement between co-twins ($R^2 = .88$, $p \leq .0001$) and between twins and their mothers ($R = .77$, $p \leq .0001$) was high for most responses. Mothers could rank the magnitude of their twins' early childhood illnesses more often than could the twins themselves (33% vs. 17%). Certain individual twins consistently made the effort to rank each experience. *Interpretation:* We conclude that subjective intra-pair rankings by twins of their early childhood health experience, especially when

validated by their mothers, can serve as a useful and informative analytic tool.

POST-PARTUM MOOD DISORDER (POSTNATAL DEPRESSION)

ICOMBO

Presenter is a member of ICOMBO, ISTS and MOA (Multiples of America) and is a physician at the University of Kentucky

Introduction: Post-Partum Mood Disorder (PPMD) is a serious illness that often goes unrecognized and untreated. This condition can range from mere 'baby blues' to a suicidal or homicidal depression and even to psychosis. *Materials and Methods:* ICOMBO conducted a survey, using Survey Monkey, of parents of twins and higher-order multiples for the occurrence of PPMD. All parents of multiples were encouraged to complete the survey, whether they had suffered from PPMD or not. *Results:* The study is ongoing but presently we have a total of 1,265 parents of twins and higher-order multiples who have completed the survey. Twelve countries so far are represented, with the majority of the responses coming from the United Kingdom, Australia, the United States and Canada. The survey is slated to be completed July 31, 2014. A recent review of the PPMD literature gave the figure of 10–15% for the rate of PPMD among new mothers. In our study of mothers of multiples, the rate was 36.2%. For those moms who had a prior singleton pregnancy, the rate of PPMD was half of that. Most were diagnosed by their family doctor and treatment generally included both medication and counseling. However, 2.7% required hospitalization and 5.7% said they could not care for their multiples for a while. Potential causes of PPMD will be discussed, as well as parental leave policies and the effects of the PPMD on the multiples. *Conclusion:* The incidence of PPMD is dramatically increased in mothers of multiples because of many factors.

STILLBIRTH RATES AND RISK FACTORS FOR STILLBIRTHS AMONG ZYGOTIC TWINS AND SINGLETONS IN JAPAN

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Introduction: We aimed to determine the stillbirth rates (SRs) for twins (monozygotic [MZ] and dizygotic [DZ]) and singletons, together with the risk factors associated with stillbirth. *Materials and Methods:* SRs were estimated using Japanese vital statistics from 1995 to 2008. *Results:* The SR for MZ twins remained nearly constant from 1995 to 2008 but significantly decreased in DZ twins and singletons, before becoming similar after 2004. The lowest SR was associated with a maternal age of 30–34 years for MZ (63.6) and DZ twins (17.1). The SRs for MZ and DZ twins were the lowest at gestational ages (GAs) of 36–39 weeks and significantly lower than those at GA ≥40 weeks. The SRs were significantly higher in like-sexed twins than in unlike-sexed twins for different birthweight (BW) groups, excluding the 1500–1999 g BW group in which SRs were comparable for female–female and male–female twins. The SR was significantly higher in MZ than in DZ twins in each birthweight discordance (BWD) category. BWD had a positive association with increased SR in MZ twins. In contrast, this relationship in DZ twins was only examined over BWD of 30% or more (7% among LB and FD twin pairs). *Conclusion:* BWD as a risk factor of SR contributed to markedly higher SR in MZ twins than in DZ twins. Increased risk of stillbirth of MZ twins was mainly attributed to twin–twin transfusion syndrome (TTTS) and birth defects. The spread of laser surgery for TTTS will reduce SR in MZ twins.

GENETIC AND ENVIRONMENTAL INFLUENCES ON TOJIKOMORI SYNDROME IN JAPAN

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Introduction: The aim of the study was to investigate the genetic and environmental influences on Tojikomori syndrome in Japan. *Background:* Tojikomori is a phenomenon in the elderly in Japan who are housebound with no physical functioning disabilities or major mental problems. Tojikomori has been defined by (1) Extent of daily activity, (2) Frequency of going out, (3) Frequency of contact with others, and (4) Mobility. And prolonged Tojikomori leads to physical dysfunction and mental problems such as depression. *Objective:* We aimed to examine the association between decrease of social activities (such as Frequency of going out and Frequency of contact with others) and depressive symptoms in twins and to explore whether genetic and environmental factors contribute to this association. *Participants:* Participants were members of the Osaka University Twin Registry. In 2008, a total of 1,422 individuals (711 twin pairs) aged 45 years and older were eligible for base line survey. We sent a questionnaire to 711 twin pairs and 906 individuals responded. In 2012, a questionnaire was sent to 906 individuals who had responded to the baseline survey in 2008 and 516 individuals responded. Among the twin pairs whose data were available for both twins in 2008 and 2012, 153 twin pairs (306 individuals) were monozygotic (60 male twin pairs and 53 female twin pairs) and 40 pairs (80 individuals) were dizygotic (28 male twin pairs, 10 female twin pairs, and 2 opposite sex pairs). *Outcome Measures:* Depressive symptoms were measured by the Japanese short version of the Geriatric Depression Scale(GDS), which has been evaluated for validity and reliability in a Japanese population. Social Activities Scores (SAS) were measured by original questions as follows: (1) How many times are you going out of your house? (Frequency of going out); (2) How many times are you talking with someone other than your housemate? (Frequency of contact with others). Raw scale scores were standardized using regression technique to adjust for the effects of age and sex. *Statistical Analysis:* Analysis 1: We used Structural Equation Modeling (SEM) analysis to evaluate the relative importance of genes and environments for the phenotypes measured (univariate SAS2008, SAS2012, GDS2008, GDS2012). Analysis 2: We used Cholesky decomposition to evaluate longitudinal effects of SAS2008 on SAS2012 and GDS2012. *Results:* All the analyses were conducted for a sample of 193 twin pairs who answered both the 2008 and 2012 surveys. There were no significant differences between MZ and DZ twins. Analysis 1: We performed SEM analysis using univariate ACE model and the AE model was the best-fitting model for SAS and GDS. Results of AE model estimate were follows. SAS(2008): a = 0.40(0.30 to 0.46) e = 0.60(0.53 to 0.67); SAS(2012): a = 0.38(0.26 to 0.43) e = 0.62(0.55 to 0.68); GDS(2008):a = 0.26 e = 0.74; GDS(2012): a = 0.28 e = 0.72; SAS(2008) was explained by 0.40 of additive genetic and 0.60 of unique environment (including err); And GDS(2008) was explained by 0.26 of additive genetic and 0.74 of unique environment (including err). Analysis 2: We performed SEM analysis using trivariate Choleskey decomposition; the path a31(A1 to 2012GDS) was 0.59 and it was higher than other additive genetic effects. *Conclusion:* (1) Frequency of social activities (such as Frequency of going out and Frequency of contact with others) is influenced by genetic factors in the elderly in Japan. (2) Association between decrease of social activities and depressive symptoms can be explained by genetic and environmental factors that are common to both phenotypes. (3) Tojikomori is a cause of future depressive symptoms and it is affected by additive genetic factor which influenced present Tojikomori.twinning

status is an important and underestimated factor in genetic counseling.

THE VARIANCE AND COVARIANCE STRUCTURE OF SOCIAL ENVIRONMENTS

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Introduction: Social worlds have significant and far-reaching effects on human physical and psychological health throughout life. Social integration and engagement are associated with improved growth and development in children, lower biological risk profiles in adults, reduced risks for cognitive and physical decline, greater resilience of somatic diseases, lower risks for disease and disability, and greater longevity. These effects are sizeable and confer as great a risk to health and mortality as do the most important known risk factors such as smoking, obesity, high blood pressure and sedentary lifestyle. Many different types of measures comprise the social environment and little is known about genetic and environmental variance and covariance structure of these measures. To gain insights into this we analyzed social integration, social strain (family and friends) and social support (family and friends) in a sample of twins participating in the Midlife in the United States (MIDUS) study. *Materials and Methods:* The data were based on information collected via the MIDUS 1 questionnaire (conducted in 1995–1996) on 907 pairs of twins aged 25–75. Five measures of social environment were studied, including Social Integration, Family Strain, Friends Strain, Family Support and Friends Support. Previous work revealed that these measures show strong psychometric properties. Univariate modeling using Cholesky decomposition was employed to analyze the variance structure of each measure and test for sex differences. On the basis of these results multivariate modeling will also be conducted to investigate the genetic and environmental covariance structure between measures. *Results:* The pattern of correlations (ranging from 0.11 to 0.46) across the measures of social environments reveals significant covariation and the magnitude of this varies between the measures of integration, support and strain. Although the univariate analyses highlight the importance of non-shared environment, the pattern of twin correlations suggest that genetic effects may explain much of the covariation. This will be further explored using multivariate modeling. *Conclusion:* Understanding the underlying sources of covariation between different aspects of social environments is important for elucidating whether the impact of social environments on health represents a general effect or is specific to certain aspects of social environments. This information will help direct further studies to look at mechanisms and potential intervention targets

NATURE OF INDIVIDUAL DIFFERENCES IN WORKING MEMORY: RUSSIAN TWIN STUDY

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Introduction: Working memory (WM) plays an important role as a system for temporarily holding and manipulating information that concern a wide range of essential cognitive tasks including learning, reasoning and comprehension (Baddeley, 1997). Working memory performance in childhood and adolescence is a strong predictor of scholastic skills, including literacy (De Jong, 1998; Swanson & Berninger, 1995) and mathematics (Bull & Scerif, 2001; DeStefano & LeFevre, 2004; Mayringer & Wimmer, 2000; Siegel & Ryan, 1989). Children with poor working memory frequently make errors in activities with big working memory demands, such as remembering instructions, concurrent processing and storage, and keeping track in multilevel tasks such as writing (Gathercole et al., 2006). *Materials and Methods:* We aimed our study to assess the impact of genetic and environmental factors on working memory. We used the Spatial Working Memory task from the computer version of the CANTAB 'Eclipse' battery of neuropsychological tests. The sample consisted of 103 monozygotic (MZ) and 106 dizygotic (DZ) twin pairs from Russia, aged from 10 to 17 years (mean age 12.92, *SD* 2.18). Model-fitting was used to estimate the contributions of genetic and environmental factors. *Results:* Cross-twin correlations of 'between errors' WM measure were 0.62 for MZ and 0.38 for DZ. The individual differences in the between errors measure were explained by additive genetic (A = 62%) and non-shared environmental (E = 38%) effects. For the 'total errors' parameter, the cross-twin correlations were 0.62 for MZ and 0.36 for DZ. The most suitable model was also genetic (A = 62%, E = 38%). 'Mean time to last response 8 boxes' measure was explained by shared environmental (C = 43%), and non-shared environmental (57%) effects. Cross-twin correlations for 'Strategy' measure were 0.44 for MZ and 0.42 for DZ. For this parameter, the most suitable model was the full model where A = 15%, C = 27%, and E = 58%. Cross-twin correlations of this measure were 0.44 for MZ and 0.32 for DZ. *Conclusion:* The results of our study suggest that genetic effects are the most important for the development of individual differences in working memory, although environmental factors influence it, especially on latency and strategy for memorization. So, we can effectively use a different training strategy for improving children's performance of working memory.

THE COLOMBO TWIN AND SINGLETON STUDY FOLLOW-UP STUDY

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Introduction: Strong evidence exists that suggests associations between cardiovascular disease, diabetes and depression. The Colombo Twin and Singleton Study follow-up Study (CoTaSS2) seeks to explore this in the Sri Lankan population and estimate the extent of overlapping genetic and environmental influences. This is the follow-up study of the population-based twin study on common mental disorders in Sri Lanka conducted in 2007. CoTaSS2 aims are to study the prevalence of depression and component phenotypes of metabolic syndrome as well as estimating the heritability of depression and exploring the genetic architecture of metabolic syndrome. *Materials and Methods:* Participants include 1,940 twin pairs (with known zygosity) and 2,019 singletons from the first twin study who are being followed up. CoTaSS2 contains multiple components: questionnaires, anthropometric and blood pressure measurements, clinical investigations, heart rate variability data and actigraphy data. A substudy within CoTaSS2 (Sleep Sub-Study) will evaluate the contribution of sleep and activity to the prevalence of metabolic syndrome and depression, and it will be the first study to determine population based estimates of sleep parameters in a developing country.A biobank containing DNA and serum from participants is being established for future genetic studies. *Results:* Data collection is ongoing, and 3,894 individual twins and 1,695 singletons have been traced up to now. The participation rates of twins and singletons are 84.35% and 67.02% respectively. *Conclusion:* Results from this study will allow us to estimate the heritability of depression and explore the reliability of lifetime diagnosis in a South

Asian population. Describing the prevalence of component phenotypes which make up metabolic syndrome, exploring the genetic architecture of metabolic syndrome phenotypes, and estimating the extent to which phenotypic correlations are explained by shared genetic or environmental effects will be done as well. We will also be able to determine whether there is a significant etiological overlap between depression and component phenotypes of metabolic syndrome.

ASSOCIATION OF HEIGHT WITH PHYSICAL AND PSYCHOSOCIAL TRAITS: THE ROLE OF GENETIC AND ENVIRONMENTAL FACTORS

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Introduction: Human height is a classic polygenic trait mainly determined by genetic factors, but it is also influenced by numerous environmental exposures in utero, childhood and adolescence. A large body of literature has reported associations of height with anthropometric, physiological and psychosocial traits, as well with the risk of several diseases. However, little is known about the background mechanisms of these associations. *Materials and Methods:* Twin and family studies offer an opportunity to analyze how genetic and environmental factors contribute to these associations. Based on the limited number of studies, this presentation provides an overview on the genetic and environmental architecture underlying covariation of height with different physical and psychosocial traits. *Results:* For example, it has been suggested that the inverse association between height and risk of coronary heart disease (CHD) observed in several populations is because of environmental factors. Higher concentration of atherogenic lipids and lipoprotein particles, one of the major risk factors for CHD, has also been related to short stature. Findings from a recent study indicated that genetic factors contribute to the covariation between height and lipoprotein profile, with genetic correlations up to -0.21. Regarding psychosocial traits, the well-documented positive association with intelligence appears to be partly explained by common genetic factors in several studies. However, the association between short stature and lower educational attainment seems to be due mainly to non-genetic family factors. *Conclusion:* Since height is an important trait from biological and social perspectives, more twin studies are needed to enhance our understanding of the genetic and environmental architecture between human height and associated traits.

EFFECTS OF GENETIC AND ENVIRONMENTAL INFLUENCES ON ABDOMINAL ADIPOSE TISSUE COMPARTMENTS AND HEPATIC LIPID ACCUMULATION: A CLASSICAL TWIN STUDY

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Introduction: In patients with diabetes and/or obesity, accumulation of abdominal adipose tissue and non-alcoholic fatty liver disease (NAFLD) are linked to increased cardiometabolic risk. Little is known about the genetic and environmental effects on the distribution of the abdominal adipose tissue compartments and hepatic lipid accumulation. The aim of the study was to assess the magnitude of genetic and environmental impact on the size of various abdominal adipose tissue compartments and the hepatic lipid accumulation within a cohort of twin pairs. *Materials and Methods:* In this classical twin study, 136 adult twin subjects (59% women; age: 57 ± 9 years, weight: 77 ± 17 kg, BMI 27 ± 5 kg/m^2[mean $\pm$ *SD*], 37 monozygotic [MZ] and 31 dizygotic [DZ] pairs) were involved. The twin pairs were investigated with a 256-slice CT-scanner. For each patient, CT-based measurement of waist circumference, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) quantification were performed. Liver and spleen attenuation was determined by calculating the average of three 300 mm2 ROIs (regions of interest). Hepatic lipid accumulation was characterized by attenuation ratios (CTL/S) and ratio of ≤ 0.9 was assessed as sign of NAFLD. Concordance between MZ and DZ pairs was assessed by Pearson correlations. For assessing heritability of abdominal adipose tissue compartments and that of hepatic lipid accumulation, the structural equation (A-C-E) model was used. *Results:* Comparing MZ to DZ twin pairs, no significant differences were found in age (55.9 ± 9.7 vs. 58.2 ± 8.8 years), in BMI (27.2 ± 3.9 vs. 26.5 ± 4.0 kg/m2), in waist circumference (94.0 ± 12.9 vs. 95.4 ± 13.1 cm), in SAT (206.0 ± 79.9 vs. 200.9 ± 8.31 cm2), in VAT (159.9 ± 91.0 vs. 143.0 ± 77.6 cm2), and in CTL/S ratio (1.1 ± 0.2 vs 1.2 ± 0.2); $p > .05$ for all comparison. Strong correlations among BMI, SAT and VAT values were found in MZ twin pairs ($r = .63$ [95% CI 0.34–0.84], $r = .74$ [95% CI 0.54–0.90], $r = .60$ [95% CI 0.34–0.79], respectively) whereas these correlations were weak or absent in DZ twin pairs ($r = .08$ [95% CI -0.34–0.43], $r = .35$ [95% CI 0.00–0.64], $r = .20$ [95% CI -0.16 – 0.51], respectively). As for hepatic lipid accumulation, correlations among CTL/S values were absent in both MZ pairs ($r = .30$, 95% CI -0,16–0.67) and DZ pairs ($r = .15$, 95% CI -0,15–0.55). Using the structural equation (A-C-E) model, relatively strong heritability index was found regarding BMI (58%, 95% CI 18–85%), SAT (74%, 95% CI 43–93%) and VAT (59%, 95% CI 22–82%) whereas environmental influences predominated in hepatic lipid accumulation (genetic effect 30% [95% CI 0–75%], shared environmental effect 1% [95% CI 0–41%], unique environmental effect 69% [95% CI 32–100%). *Conclusion:* Both BMI and abdominal adipose tissue compartments (SAT and VAT) have relatively strong heritability whereas hepatic lipid accumulations (presence of NAFLD) is predominantly influenced by environmental factors.

THE CLINICAL CASE OF PARASITE OMPHALOPAGUS

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Introduction: Multiple pregnancies account for 0.7–1.5% of all pregnancies, which can be complicated by delayed growth of one or both fetuses, twin-twin transfusion syndrome (FFTS), intrauterine death of one or both fetuses. The fetus in fetus or a parasitic twin is a rare anomaly in multiple pregnancies. This malformation is a variant of conjoined twins and occurs only 1 time for a half a million births of delivery and only in monoamniotic monochorionic monozygotic twins. The ratio of boys to girls is 1.3:1. *Materials and Methods:* Due to the rarity of occurrence of this disease, it is interesting to present this clinical case of parasite omphalopagus. *Results:* Child A. Pregnancy — 1, childbirth — 1. Heredity on the congenital malformation was not found; the parents did not have bad habits and occupational exposures. Congenital malformation of fetus was found prenatally by ultrasound (27–28 weeks). Births in period 35–36 weeks. A boy was born weighing 3116 g with Apgar scores of 6–7 point. Locally: the extra fetus was visually determined from the belly of the child; the visible part of the 'fetus-parasite' was presented with torso, pelvis, two lower limbs, with the vestigial appendage of the only upper limb; external sexual characteristics developed by male pattern, and both testicles were not palpable. There was an excretion of bright urine from the penis, but there was no anus.There was no motor activity, tactile and pain sensitivity. The place of joining was

a slit-like hole measuring 7.5 × 5.5 cm. According to the results of instrumental studies we revealed the absence of joint internal organs. At the age of 21 days, surgery was performed on the child to remove the parasite omphalopagus. Intraoperatively, we determined that the nutrition of the extra fetus was carried by additional vessels coming from the umbilical vessels of the child. Fourteen days after surgery the patient was discharged from the hospital in a satisfactory condition. In catamnesis the child grows and develops according to his age. *Conclusion:* The prognosis for conjoined twins depends on the location and the extent of their connection and the presence of the related malformations. The prenatal diagnosis of conjoined twins and delivery at a specialized medical institution promotes the timely provision of qualified surgical neonatal care, which will reduce the death rate for children with this malformation.

GENETIC AND ENVIRONMENTAL SOURCES OF PERSONALITY DEVELOPMENT AND WELLBEING IN OLD AGE

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Introduction: Even though there is abundant evidence that personality development continues in adulthood due to both genetic and environmental factors, little is known about the genetic and environmental contributions to personality change in old age. We thus investigated the genetic and environmental sources of rank-order continuity and change in several personality traits (neuroticism, extraversion, openness, agreeableness, conscientiousness, perceived control, and affect intensity) and wellbeing. In addition, we analyzed the interrelation between change in personality traits and wellbeing change. *Materials and Methods:* We analyzed data from older adult twins, aged 64–85 at time 1 (N = 410; 91 female and 43 male MZ and 42 female and 21 male DZ twin pairs), captured at two different time points about 5 years apart. To estimate the genetic and environmental influences on individual differences in level and change, we ran latent change twin model analyses. These twin models allow the disentanglement of additive genetic factors from environmental factors shared and not shared by twins controlled for non-random method (due to parcel-specific biases) and random error variance. We also ran a series of bivariate latent autoregressive models allowing for estimations of prospective effects from personality traits to wellbeing and vice versa controlled for initial correlations between the variables and their specific rank-order continuity. *Results:* On average, neuroticism increased, whereas extraversion, conscientiousness, and perceived control significantly decreased over time. Change in perceived control occurred with changes in neuroticism and conscientiousness, pointing to particular adaptation mechanisms specific to old age. Individual differences in personality traits were fairly stable due to both genetic (on average 59%) and environmental factors (on average 41%). Individual differences in change were primarily due to environmental sources beyond random error (on average 57%). Model fitting results also suggest genetic contributions to changes in extraversion (97%), conscientiousness (62%), openness (59%), agreeableness (41%), and perceived control (45%). Even though the average level of wellbeing did not significantly change over time, individual wellbeing tended to decrease, with strongly increasing levels of neuroticism and decreasing extraversion, conscientiousness, and perceived control. *Conclusion:* Results suggest average personality change in old age that goes in the opposite direction compared to the age trends typically reported for younger and middle-aged adults. Opposite trends in old age can be explained by different developmental and adaptation strategies (i.e., selection, optimization, and compensation). Even though individual differences in personality traits are largely stable over time, personality can change and individuals differ in change in old age. Genetic as well as environmental sources affect both continuity in individual differences and variation in intraindividual change, indicating that multiple sources — which may be correlated and interact in complex ways — drive personality development and differential plasticity in old age. The nature of the interrelation between personality traits and wellbeing in old age appears to be primarily unidirectional indicating that personality change predicts change in wellbeing.

COTININE AS A BIOMARKER FOR TOBACCO USE

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Introduction: Quantitative genetic studies indicate clear genetic influences on smoking behavior. Self-reported smoking behavior is error-prone, and biomarkers of smoking can provide more accurate measures of nicotine intake. While nicotine has a short half-life of 2 h, its main metabolite is cotinine, which has a half-life of 16 h. Overall, the metabolism of nicotine is quite complex with multiple genes influencing the relevant pathways. The few laboratory studies of such biomarkers in twins indicate substantial genetic influences on the rate of metabolism of nicotine metabolites, but estimates from free-living populations are rare. *Materials and Methods:* I will review twin studies of cotinine and its metabolism in the talk, and show that findings from gwas studies support the major impact of genetic factors. Non-smoking related risk factors also influence the metabolism of nicotine and cotinine. These include age, sex, obesity and alcohol use, which need to be considered in genetic analyses as well. If both cotinine and its major metabolite, 3-hydroxycotinine, are measured, the Nicotine Metabolite ratio (NMR), a measure of nicotine metabolism speed, can be computed. NMR is associated with amount smoked and ability to quite smoking. *Results:* Our own studies of cotinine have been based on serum samples from smoking and non-smoking twins ($n = 1300$ samples). In the FinnTwin12 study, information on smoking behavior and nicotine dependence were obtained from questionnaires and interviews of these young adults (mean age 22, range 21–24). In the FinnTwin16 study, twin pairs concordant and discordant for alcohol problems were studied (with a mean age of 26.2 years, range 23–30). For regular smokers, nicotine metabolites, cotinine and 3-hydroxycotinine, were assayed by liquid chromatography with tandem mass spectrometry. Overall, the estimated heritabilities for cotinine and NMR were 0.64 and 0.80. *Conclusion:* We may conclude that among young adult twin pairs in the population, the heritability of cotinine levels and NMR is high. Differences between twins can be used to examine environmental determinants.

EVOLUTION OF STAGE 1 TWIN-TO-TWIN TRANSFUSION SYNDROME: COHORT STUDY AND META-ANALYSIS

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Introduction: The data on progression and survival in stage 1 twin-to-twin transfusion syndrome (TTTS) are controversial. The main aim of this cohort study was to ascertain the progression and the survival of twin pregnancies complicated by stage 1 TTTS managed in our centre, and to conduct a systematic review of cases reported in the literature. *Materials and Methods:* This was a retrospective cohort study of stage 1 TTTS cases identified at our centre. TTTS cases were classified according to Quintero staging. Laser therapy was offered in cases that progressed to a higher stage or in case of increasing severity of the maternal discomfort.

Pregnancy management and outcomes were ascertained from maternal and neonatal records. We also performed a systematic review of the literature on the progression and survival in twin pregnancies complicated by stage 1 TTTS. MEDLINE, EMBASE, Cinhal and the Cochrane Library were searched electronically using the relevant mesh terms. Between-study heterogeneity was assessed using the I2 test. *Results:* The analysis included 41 cases of stage 1 TTTS with complete follow-up data. The incidence of progression, regression and stable course were 54%, 24% and 22%, respectively. Most of the cases which progressed developed stage 3 TTTS, and the interval from assessment to progression was up to 3 weeks in the majority of cases. Most of the cases which progressed were treated using laser ($n = 20$). The rates of double survival and survival of at least one fetus were 64% and 91% in the cases which progressed, while the corresponding rates in the cases which did not show progression were 95% and 100%, respectively, 94.4% and 100% with conservative management, and 60% and 90% following laser treatment, respectively. The overall double survival rate was 78%, while at least one survival was 95%. There was no significant difference between the cases which progressed and those which did not, in the estimated fetal weight discordance, amniotic fluid discordance or gestational age at the initial assessment. The literature search yielded 1,228 citations, of which 20 studies were included. The pooled incidence of progression was 0.33 (95% CI 0.20–0.47). The double survival and survival of at least one fetus in TTTS cases which had expectant management were 0.76 (95% CI 0.54–0.92) and 0.91 (95% CI 0.71–1.00), respectively. The corresponding figures in TTTS cases which had fetal therapy were 0.70 (95% CI 0.62–0.77) and 0.87 (95% CI 0.79–0.93) with amnioreduction, 0.75 (95% CI 0.66–0.84) and 0.90 (95% CI 0.85–0.94) in those who had laser as a first line treatment, 0.65 (0.57–0.73) and 0.87 (0.81–0.92) in those who had laser in cases which progressed. *Conclusion:* The progression rate in stage 1 TTTS is significant and warrants close monitoring. The meta-analysis suggests that the rate of survival of at least one twin is similar for conservative and laser treatment. However, the literature might be biased by the fact that cases which progress, are more likely to be offered laser treatment. The initial management of stage 1 TTTS remains in equipoise.

CEREBROPLACENTAL RATIO AND PERINATAL MORTALITY IN MONOCHORIONIC TWIN PREGNANCIES

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Introduction: Monochorionic diamniotic (MCDA) twin pregnancies are associated with increased risk of perinatal mortality and morbidity. Cerebroplacental ratio (CPR) has a role in predicting adverse outcome in singleton pregnancies complicated by small for gestational age. Recently, the utility of CPR was also reported in pregnancies with average for gestational age newborn. The main aim of this study was to investigate the role of CPR in MCDA twin pregnancies. *Materials and Methods:* This was a retrospective cohort study in which routine fetal biometry, umbilical artery (UA) and middle cerebral artery (MCA) Doppler were recorded at the same visit. CPR was calculated as the ratio between MCA pulsatility index (PI) and UA PI. Estimated fetal weight discordance (EFWD) was calculated as (larger EFW-smaller EFW)/larger EFW. CPR discordance (CPRD) was calculated as (higher CPR-lower CPR)/higher CPR. The chorionicity was confirmed in all cases by placental examination. Pregnancy outcomes were ascertained from the obstetric and neonatal records. MC monoamniotic twin pregnancies, cases with structural abnormalities, aneuploidy, pregnancies complicated by twin-to-twin transfusion syndrome (TTTS) or twin reversed arterial perfusion were excluded. Regression analysis was used to investigate the relationship between CPRD, EFWD and perinatal death. The screening performance was determined by ROC curve analysis. *Results:* The analysis included 224 MCDA twin pregnancies. Perinatal death occurred in 19 (8.5%) pregnancies. The median (IQR) CPRD was significantly higher in the pregnancies complicated by perinatal mortality compared to those that were not (68.2; 32.6–85.9 vs. 19.7%; IQR 9.0–34.8, $p = .01$). Similarly, the median (IQR) EFWD was significantly higher in pregnancies complicated by perinatal mortality compared to those that were not (30.7; 16.8–48.4 vs. 9.7%; IQR 4.7–18.0, $p = .002$). Both CPRD and EFWD were significantly associated with the risk of perinatal death (OR 1.07; 95% CI 1.02–1.12, $p = .004$ and 1.06; 95%CI 1.02–1.10, p .002, respectively). Logistic regression showed that CPRD was an independent predictor of perinatal death, even after adjusting for EFWD (adjusted OR 1.05, $p = .043$). Both CPRD and EFWD were significant predictors of perinatal death (AUC 0.88; 95% CI 0.73–1.02 and 0.83; 95% CI 0.69–0.96, respectively; $p = .01$). The best cut-off CPRD was 50.9%, which was associated with a sensitivity of 75%, specificity of 88.1% and positive likelihood ratio (+ ve LR) of 6.33. The best cut-off EFWD was 23.9%, which was associated with a sensitivity of 75.0%, specificity of 85.0% and + ve LR of 5.01. *Conclusion:* CPRD is associated with the risk of perinatal death in MCDA twin pregnancies, even after adjusting for EFWD. MCDA twin pregnancies with CPRD greater than 50% require careful monitoring.

PREDICTION OF MONOCHORIONCITY-RELATED VASCULAR COMPLICATIONS IN TWIN PREGNANCIES PRESENTING WITH AMNIOTIC FLUID DISCORDANCE

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Introduction: Up to 25–30% of monochorionic diamniotic (MCDA) twin pregnancies are complicated with severe twin-to-twin transfusion syndrome (TTTS) or selective intrauterine growth restriction (sIUGR). MCDA twin pregnancies presenting with amniotic fluid discordance (AFD) are closely monitored for the development of TTTS. Stratification of their risk would allow surveillance to be tailored appropriately. The aim of this study was to assess the predictive value of ultrasound for the development of monochorionicity-related vascular complications, including TTTS and selective intrauterine growth restriction (sIUGR) in pregnancies with moderate AFD (mAFD). *Materials and Methods:* This was a retrospective cohort study of twin pregnancies presenting with moderate AFD, defined as any obvious AFD not fulfilling the criteria for TTTS ($n = 102$). AFD was calculated as deepest vertical pool (DVP) Twin 1 – DVP Twin 2. AFD. Estimated fetal weight discordance (EFWD) and umbilical artery (UA) Doppler were assessed in these pregnancies at each visit. The chorionicity was confirmed in all cases by placental examination. MC monoamniotic twin pregnancies, cases with structural abnormalities, aneuploidy or twin reversed arterial perfusion were excluded. Regression analysis was used to investigate the variables associated with pregnancy outcomes. The screening performance was determined by ROC curve analysis. *Results:* MC-related vascular complications developed in 78 (76.5%) pregnancies (46 TTTS and 38 sIUGR). Laser treatment was performed in 31 cases, while amnioreduction was performed in 2. The median (IQR) EFWD was 15.7% (9.4–27.5), 19.7% (14.7–28.2) and 11.6% (4.2–18.0) in the pregnancies that developed TTTS, sIUGR and those who did not develop MC-related vascular complications, respectively ($p < .01$). The median (IQR) gestational age (GA) at the initial presentation was 17.1 weeks (16.6–19.1), 19.4 weeks (17.1–23.7) and 19.4 weeks (17.7–24.1) in the pregnancies that developed TTTS, sIUGR and those who did not develop MC-related vascular complications, respectively ($p < .01$). AFD and GA at the initial assessment were significantly associated with the development of TTTS (adjusted OR 1.59; 95% CI 1.12–2.26, $p = .009$ and 0.81; 95%CI

0.70–0.93, p .004, respectively). Absent or reversed end-diastolic flow (AREDF) in the UA of twin 2 at the initial assessment was significantly associated with the development of sIUGR (adjusted OR 4.58; 95% CI: 1.22–17.17, $p = .024$). However, the predictive accuracy of these markers was poor for TTTS or sIUGR (AUC 0.66; 95% CI 0.56–0.77 for AFD and TTTS; and 0.58; 95% CI 0.50–0.65 for twin 2 UA AREDF).

Conclusion: The risk of MC-related vascular complications in MCDA twin pregnancies presenting with moderate AFD is high. The GA at presentation and the severity of AFD were associated with the development of TTTS, while AREDF in the UA in twin 2 was associated with sIUGR. However, their predictive value is poor.

CROWN-RUMP LENGTH DISCORDANCE AND FETAL STRUCTURAL ABNORMALITIES IN TWIN PREGNANCIES

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Introduction: The prevalence of fetal structural abnormalities is higher in twin, compared to singleton, pregnancies and is reported to be higher in monochorionic (MC) than in dichorionic (DC) twin pregnancies. Fetuses with structural abnormalities or aneuploidy are more likely to have a smaller crown-rump length (CRL). CRL discordance is associated with an increased risk of adverse pregnancy outcome in twin pregnancies. However, most studies have excluded cases with fetal structural abnormalities or aneuploidy. The aim of this study was to investigate the performance of CRL discordance in the prediction of major congenital anomalies. *Materials and Methods:* This was a cohort study of twin pregnancies of known chorionicity in a tertiary centre. MC monoamniotic twin pregnancies, pregnancies with single or double loss at the time of the scan, those complicated by twin-to-twin transfusion syndrome, twin reversed arterial perfusion or conjoined twins were excluded. Pregnancy outcomes were ascertained from obstetric and neonatal records. Logistic regression and ROC curve analyses were performed to evaluate the contribution of CRL discordance in determining the risk of structural anomalies. *Results:* The analysis included 911 twin pregnancies (241 MC and 670 DC). Of these, 85 (9.3%) pregnancies were complicated by structural anomaly and 13 had aneuploidy. The prevalence of structural abnormalities was 10.8% and 8.8% of MC and DC twin pregnancies, respectively. CRL discordance of 10% or greater was present in 14.8% of this cohort. The prevalence of fetal structural anomalies was higher in the group with CRL discordance of 10% or greater than in the group with CRL discordance <10% (19.3% vs. 7.6%, $p < .001$). The corresponding figures were 12.5% and 23% in MC and DC twin pregnancies, respectively. Logistic regression analysis demonstrated that CRL discordance (adjusted OR 1.07; 95% CI 1.04–1.11, p3.5mm, which is the 99th centile) (adjusted OR 5.52; 95% CI 2.12–14.38, $p < .001$) were independently associated with the risk of structural anomalies. This significant association persists even after adjusting for individual fetal size ($p < .001$ for both). The area under the ROC curve was 0.61 (95% CI, 0.54–0.68). At a cut-off value of 10% for CRL discordance, the sensitivity and specificity were 31.8% and 86.6%, while the + ve and –ve likelihood ratios were 2.36 and 0.79, respectively. *Conclusion:* CRL discordance is associated with an increased risk of fetal structural defects. The presence of CRL discordance noted at the time of the ultrasound scan should alert the sonographer of the need to rule out major structural anomalies. However, its predictive value is poor.

THORACO-OMPHALOPAGUS CONJOINED TWINS DIAGNOSED AT 14 WEEKS OF GESTATION

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Introduction: Conjoined twins are very rare and the mortality rate of the fetus is extremely high. Early prenatal diagnosis is crucial, as it provides the opportunity for the mother and father to help in recognizing the conjunction of the twins and to help medical team in defining the prognosis of conjoined twins. *Results:* We present a case of thoraco-omphalopagus conjoined twins diagnosed by 2-dimensional and 3-dimensional transabdominal sonography at 14 + 2 weeks of gestation. *Conclusion:* Assessing conjoined twins' structural integrity or malformations is important in order to completely understand the anomalies. The prognosis for conjoined twins is typically poor and as such, prenatal diagnosis of must be emphasized.

GENETIC AND ENVIRONMENTAL EFFECTS ON FAT DISTRIBUTION: THE HEALTHY TWIN STUDY

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Introduction: People commonly think that individuals have different fat distribution and that this characteristic is inherited. Also, there are a variety of methods on managing regional fat. However, most fat distribution studies are actually not about regional fat but about abdominal fat. In the case of abdominal obesity, this is the leading cause of obesity-related diseases. As a result, researchers have mainly studied abdominal fat and studies of fat distribution in other areas are very poor. *Materials and Methods:* The twin cohort study in Korea consists of 3,461 individuals including 689 families, 550 pairs of identical twins, and 124 pairs of dizygotic twins. From this cohort, 3,435 people were measured by dual-energy X-ray absorptiometry (DXA). The fat regions of participants used in this study were arms, legs, head, and trunk. To investigate the correlation with fat mass and obesity indices, we used Spearman correlation analysis. The association with regional fat distribution and several environmental factors was analyzed using multiple regression with a mixed model. Genetic factor that have effects on regional fat distribution was analyzed by two methods: intraclass correlation coefficients(ICC) and heritability analysis using variance component model. *Results:* Correlation between fat distribution and waist hip ratio, which is an important indicator of abdominal obesity, was small and the portion that environment has effects on regional fat distribution was small. However, although several environmental factors were not associated with regional fat, genetic factors have a strong association with regional fat. This could be confirmed by ICC analysis and heritability analysis. Especially because total fat was correlated with regional fat, this explained a large portion of regional fat in heritability analysis. But, after the effects of total fat were excluded, additive genetic effects still accounted for the remaining effects on fat distribution. This means that genetic factors, among several factors, have significant effects on regional fat distribution; the common idea that there is s genetic predisposition to gain fat in a particular region can be proved to some extent. Until now, although the research has been done mainly on central obesity,

the results on regional fat distribution in this study could help us to understand more overall fat distribution among Koreans. *Conclusion:* According to these results, there re strong genetic effects on regional fat distribution. Further study on the association between fat distribution and hormones, or genome-wide association study on regional fat distribution, could be investigated. These follow-up studies will be able to provide some direction on managing regional fat.

CHANGES OF MULTIPLE PREGNANCIES; DUTCH TRENDS OVER THE DECADE 1994 THROUGH 2011

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Introduction: Over the past decades there has been a large increase of multiples in the Netherlands as in many other developed countries. This increase has been associated with the introduction of artificial reproductive therapies (ART) such as in vitro fertilization (IVF), intra uterine insemination (IUI) and ovulation induction (OI). Multiple pregnancies are often seen as a complication rather than a success, because of the association with pregnancy complications endangering mothers' health as well as the fetus's health. Reducing the number of embryos to be transferred is a simple solution to the problem of multiples in IVF/ICSI treatments. In IUI/OI therapies this is more complicated as only the number of follicles can be influenced. The following fertilization and implantation is out of our hands. It is important to keep a close trace of trends regarding multiple pregnancy rates in relation to the various conception modes, including natural conception. *Materials and Methods:* The Netherlands has a national obstetric registration of all hospital deliveries from which the relation between multiples and way of conception can be extracted. Since 1994 it is mandatory to report on the means of conception: IVF/ICSI, OI/IUI or natural conception. The data are representative for the Netherlands as all hospitals participate in the registration and all twins are born in hospitals. Data for a period of over 15 years was analyzed on the relation between multiples and means of conception. The data contains information on all twins and other multiple deliveries from the amenorrhea of 16 weeks on, divided by the means of conception and divided by equal and unequal gender. Twins of unequal gender were considered dizygotic twins. According to the calculations of Weinberg (the Weinberg rule) the estimated number of total dizygotic twins is the amount of unequal gender twins multiplied by two. We used data about the total number of deliveries in the examined years of the Central Bureau for Statistics (CBS) in the Netherlands in order to calculate prevalence of twin births (www.cbs.nl). *Results:* From 1994 to 2001 there has been a strong increase of twin births (46%). The largest increase came from natural conception. Second, IVF/ICSI contributes to twin pregnancies (20–25%) and finally OI/IUI with 10–15%. This last category shows a slight increase since 1995. Since 2001, the number of twin deliveries has steadily declined. In particular, twins from IVF/ICSI declined by as much as 45%. Total numbers of naturally conceived dizygotic twins per total deliveries shows an ongoing increase until 2006. This large increase is probably the result of the gradually increasing maternal age, which has increased from 30.6 to 32 years. From 2006 we can see a continuous decrease in the amount of naturally conceived dizygotic twins, together with maternal age. In a demographic respect, this should be considered an earth shift. From 2006 a continuous decrease of naturally conceived dizygotic twins can be seen together with a decline of maternal age. These numbers compared to numbers of the CBS before IVF existed (<1981), showing that an increase of 1 year in maternal age equals a 1 pro mille increase in twin pregnancies. *Conclusion:* When IVF treatment was implemented during the 1980s, there was a rapid increase of multiple births. Until several years ago it was general practice to place more than two embryos back in order to increase the chances of pregnancy. New insights and techniques in the IVF laboratories on embryo selection and improved cryo preservation mean that nowadays it is advantageous to transfer a single embryo without significantly decreasing the chance on pregnancy. Ever since, a regular decline in multiples after IVF treatment has been observed. It should be noted that during the past 15 years, most higher order multiples resulted from natural conception. Increasing age, decreasing fertility, yet increasing chance of multiples seems a paradox. A recently published paper shows that older women have a higher chance of developing spontaneous multiple follicle growth, hence the increased chances of multiple ovulations, fertilization and pregnancy. Apparently, this multiple follicle growth is a result of change in the ovarian-pituitary feedback mechanism. Due to a decline in oocyte supply, Inhibin B decreases and FSH will increase causing ongoing multiple follicle growth. Reducing the mean maternal age will cause a considerable reduction in natural conception multiple pregnancies, likely with health economic implications.

STUDY DESIGN: AMYLOID PATHOLOGY IN COGNITIVELY NORMAL ELDERLY TWINS

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Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder characterised by progressive neuronal loss and eventually death. Abnormal aggregation of beta amyloid (Aβ) is the first event in AD and is present in 20–40% of cognitively normal elderly. After amyloid aggregation, neuronal injury develops. The concordance of monozygotic twins for a clinical diagnosis of AD-type dementia is 0.40–0.67. This suggests a major genetic role in the development of AD but also involvement of environmental factors. Until now little was known about concordance of AD biomarkers. The main objective is to determine the concordance of amyloid and neuronal injury AD biomarkers and the combination of both in monozygotic twins and the appearance of AD biomarkers in relation to cognitive decline and/or diagnosis. We hypothesize that concordance rate will be higher for amyloidmarkers than for neuronal injury markers. We will also test whether discordance is associated with gene expression and DNA methylation. *Materials and Methods:* We will perform a longitudinal observational cohort study of 100 monozygotic twin pairs aged 60–100 years from the Netherlands Twin Registry (NTR). At baseline, the participants will undergo cognitive testing (CANTAB and paper-pencil tests), assessment of functional impairment, depression, quality of life, sleep quality, and physical examination, magnetoencephalography (MEG), Magnetic Resonance Imaging (MRI, including structural MRI, FLAIR, arterial spin labelling [ASL], resting state, and DTI and SWI sequences), [18F] Flutemetamol positron emission tomography (PET), retinal imaging, Ocular Coherence Tomography (OCT), duplex of the carotid arteries and analysis of cerebrospinal fluid (CSF) and blood (plasma, serum, RNA, DNA methylation). Cognitive testing will be performed again after 2 years. *Results:* The study will start in August 2014. As

beta amyloid markers, we determine amyloid pathology as assessed by CSF analysis or PET scan. As injury markers we will test tau in CSF, neuropsychological, clinical markers, functional and structural brain connectivity as assessed by MEG and MRI, brain atrophy as assessed by MRI, and vascular changes as assessed by MRI, retinal imaging or duplex of the carotid arteries. *Conclusion:* The degree of gene expression and DNA methylation markers will be compared between concordant and discordant cases.

CARBETOCIN FOR POST-PARTUM HEMORRHAGE PREVENTION IN TWIN PREGNANCY

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Introduction: Prevention of post-partum hemorrhage (PPT) is a major issue in decreasing maternal mortality and morbidity. It is defined as a blood loss more than 500 mL after vaginal delivery and more than 1000 mL after cesarean section during the first 24 hours after the labor. One of the major causes of PPT is uterine atony. Carbetocin is a synthetic long-active oxytocin analogue. It may be used for PPT prevention during cesarean delivery in patients with risk of uterine atony, such as multiple pregnancy. The aim of this study was to compare the efficacy of a single dose of intravenous 5 IU of oxytocin and 100 mcg of carbetocin in terms of blood loss and the need of additional uterotonic agents use during cesarean section in twin pregnancy. *Materials and Methods:* A retrospective analysis of 86 patients with twin pregnancies, hospitalized at 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, between 2012 and 2013 was conducted. Since 2013 all patients were administered carbetocin for PPT prevention during cesarean section. The study group consisted of 40 patients with carbetocin administration and the control group of 46 patients with oxytocin administration. The prevalence of post-partum hemorrhages, hemoglobin concentration before and after delivery, and additional uterotonic management were analyzed in both groups. *Results:* There were no differences between the groups concerning patients' age (average 32.3 years in the study group vs. 32.2 in the control group), duration of pregnancy (35.3 Hbd vs. 35.4 Hbd), body mass index (23.8 vs. 22.2), parity (52% primipapas vs. 74%), chorionicity (30% monochorionic vs. 25%), hemoglobin (12.3 G/L vs. 12 G/L), platelets (174 G/L vs. 171 G/L) or fibrogen concentration (544 mG/L vs. 501 mG/L) before the cesarean delivery, percentage of elective cesarean sections and total neonatal birthweight. The prevalence of post-partum hemorrhage was similar in both groups (12% vs. 13%). The mean hemoglobin concentration after the cesarean section was higher in the study group (11.4 G/L vs. 10.9 G/L) and the difference was close to significant ($p = .068$). In the control group additional uterotonic agents were used significantly more often (67% vs. 25% in study group; $p = .001$). The only case of B-Lynch suture use was in the control group. There were no cases of hysterectomy or packed red blood cells transfusion in both groups. *Conclusion:* Carbetocin might be useful for post-partum hemorrhage prevention in twin pregnancy.

PREGNANCY COMPLICATIONS IN TWIN GESTATION

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Introduction: It is known that multiple pregnancies are at increased risk of pregnancy complications and higher neonatal mortality and morbidity. The aim of this study was to evaluate the frequency of particular complications in twin gestation. *Materials and Methods:* A retrospective analysis of medical data of 233 patients in twin pregnancies, who delivered at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw between 2008 and April 2014, was conducted. The incidence of pregnancy complications in monochorionic and dichorionic twins was evaluated. *Results:* 85.4% of all pregnancies were dichorionic (DC), 14.6% monochorionic (MC), including 1.7% monoamniotic pregnancies. 42.7% of DC and 8.8% of MC pregnancies were conceived by assisted reproduction; 16.3% of all patients suffered from first trimester bleeding. Gestational diabetes occurred more often in MC pregnancies (20.6% vs. 13.6%; 14.6% of all patients), but the difference was not significant. Pregnancy cholestasis was also more often in MC group (14.7% vs 6%; overall 7.3%; $p = NS$). Pregnancy-induced hypertension occurred almost twice more often in the DC group (10.6% vs. 5.9%; overall 9.9%; $p = NS$). Complications specific for MC gestation (TTTS and TRAP) occurred in 8.8% of cases. Intrauterine growth restriction of at least one twin occurred in 20.6% of all pregnancies, and significantly more often in the MC than the DC group (44.1% vs. 16.6%; $p = .0002$). 63.7% of all patient delivered preterm. Premature rupture of membranes occurred in 21.6% of DC pregnancies and in 11.8% of MC pregnancies, but the difference was not significant (overall 20.2%). 67.8% of the DC group and 73.5% of the MC group were delivered before spontaneous onset of labor due to medical reasons. Significantly, more patients in the monochorionic group delivered < 37 weeks of pregnancy (79.4% vs 61.3%; $p = .042$). In both groups, the majority of preterm labors were late preterm (41.1% DC vs. 41.2% MC). Preterm births <32 weeks of gestation occurred in 17.6% of MC twins and 11.5% of DC twins ($p = NS$).The mean neonatal birth weight in MC group was 2058g ($\pm$635) vs. 2360g ($\pm$608) in DC group ($p = .008$). *Conclusion:* Although pregnancy complications are frequent in twin pregnancies, preterm delivery remains the major problem. In MC twins it seems to be related to pregnancy complications, while in DC twins to spontaneous onset of labor.

INHERITANCE OF LEFT VENTRICULAR DEFORMATION

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Introduction: Although prognostic value of left ventricular (LV) deformation parameters is widely recognized, data on their determinant factors are still scarce. To date, no study has investigated the impact of genetic and environmental effects on left ventricular deformation profile. *Materials and Methods:* We recruited 51 twin pairs (22 monozygotic and 29 same-sex dizygotic twin pairs, mean age 56 ± 9 years). Siblings with coronary artery disease, any cardiomyopathy or severe valvular disease were not included. Beyond standard echocardiographic protocol, parasternal short axis- and apical views optimized for speckle tracking analysis were obtained. Using dedicated software (TomTec 2D Cardiac Performance Analysis), global circumferential (GCS), longitudinal (GLS) and radial (GRS) strains were calculated by averaging the segmental values of the 16 LV segments. Apical counter-clockwise, basal clockwise rotation and their net difference, the LV twist were also measured. *Results:* The intraclass correlation coefficients for GCS were 0.94 for monozygotic twins (95% CI: 0.89–0.98) and 0.34 for dizygotic twins (0.18–0.52). After adjusting for age and sex, the univariate additive genetic (A), common (C) and unique (E) environmental

effects model showed 94% genetic component in the variance of GCS (88 to 98%). Similarly high, but dominant genetic effects (D) were found regarding GLS, GRS, apical rotation, basal rotation, and twist (D: 91, 87, 81, 91 and 88%, respectively). Unique environmental effects were responsible for the rest of the variance (E: 6–19%). Common environment had no influence on these variables. *Conclusion:* Our study demonstrated a very dominant heritability of the LV deformation parameters with similar strength in all directions. Role of common and unique environmental factors is scant. These results urge to search for the responsible genes determining LV deformation.

WHAT HAVE WE LEARNED FROM TWIN STUDIES ABOUT LEARNING?

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Introduction: Twin research into educationally relevant traits has moved beyond estimating the relative contributions of genetic and environmental factors to individual differences. Many important findings have recently emerged from this research, suggesting that the etiology of individual differences in motivation, ability and achievement is multifactorial, dynamic, and complex. *Materials and Methods:* The results presented in this talk come from several recent investigations based on collaborating large twin studies in six countries, providing a unique platform for a cross-cultural genetically informative approach to the study of educationally relevant traits. Data on children's academic motivation, emotion, ability and achievement have been analysed in the context of development and different cultural settings. *Results:* A number of unexpected results emerged. For example, academic achievement — such as performance in reading, language and mathematics — has been found to be highly heritable throughout school education, whereas heritability of general cognitive ability has been found to be only moderately heritable in the early school years. Heritability of general cognitive ability has also been shown to increase gradually, reaching substantial levels in adulthood. Active gene-environment correlations, whereby children experience, modify, and select their environments differently, depending in part on their genetic uniqueness, may contribute to the observed increase in heritability of IQ. Another finding from several large-scale twin studies suggest that the extent to which family members show similar levels of academic motivation and enjoyment comes from their shared genetic makeup. On the contrary, the dissimilarities between family members largely come from individual-specific environments. Twin data from six different countries showed that shared family or school environments do not contribute to similarity of family members in their academic motivation. Twin studies have also showed a large degree of overlap in genetic factors influencing different learning abilities and disabilities, suggesting that discrepancies in an individual's performance across different academic disciplines largely stem from environmental factors. *Conclusion:* Twin method is an invaluable tool in the study of child development. Recent behavioral genetic studies suggest that, contrary to common opinion, genetic effects on leaning ability and achievement are not static or deterministic, but change throughout life and in different educational and cultural contexts. Behavioral genetic research into the etiology of individual differences in learning contributes to a long-term goal of developing personalized educational methods suitable for each learner.

DNA EVIDENCE CONFIRMS AND EXPANDS RESULTS OF TWIN STUDIES: EDUCATIONAL ACHIEVEMENT AS AN EXAMPLE

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Introduction: Educational achievement is one of the best predictors of important life outcomes such as education, occupation, mental and physical health and illness, and mortality. Twin studies have shown that individual differences in educational achievement are substantially heritable. Indeed, we have demonstrated that educational achievement is significantly more heritable than intelligence in the early school years. These findings are being confirmed by the first new quantitative genetic technique in a century — Genome-wide Complex Trait Analysis (GCTA) — which estimates genetic influence using genome-wide genotypes in large samples of unrelated individuals. *Materials and Methods:* Here, we apply GCTA to millions of single-nucleotide polymorphisms to estimate pair-by-pair genetic similarity for 3,000 unrelated children from a UK-representative sample for whom we also have data on children's educational achievement on a national examination at the end of compulsory education at age 16. *Results:* Comparing heritability estimates from GCTA and the twin method confirms the results of twin studies and reveals important insights into the genetic architecture of educational achievement.

INCREASED BREAST CANCER RISK AFTER A MULTIPLE PREGNANCY IN IVF-TREATED WOMEN: A NATIONWIDE DUTCH COHORT STUDY

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Introduction: Breast cancer risk is temporarily increased after a full-term pregnancy and declines thereafter, possibly due to increased levels of gonadal and placental hormones during pregnancy. Inconsistent results, however, have been reported after twin pregnancies with higher hormone levels. Among women treated with in-vitro fertilization (IVF), for whom the number of embryos available for implantation is known, we recently observed that a multiple birth after implantation of all transferred embryos is associated with higher levels of vascular endothelial growth factor (VEGF). As VEGF is involved in breast cancer progression, we studied the effects of embryo implantation and a multiple birth on breast cancer risk in a nationwide Dutch cohort of IVF-treated women. *Materials and Methods:* We performed a cohort analysis among 12,589 women who had been treated with IVF between 1983–1995 and completed a risk factor questionnaire between 1997–1999. Data on IVF treatment were obtained from medical records. Breast cancer cases were ascertained through linkage with the population-based Netherlands Cancer Registry. Breast cancer risks associated with singleton and multiple births were estimated with Cox regression. *Results:* There were 1,688 women (13.4%) with multiples, 6,027 (47.9%) with singletons, and 4,874 (38.7%) nulliparous women. Breast cancer occurred in 317 women, of whom 57 had multiples. Breast cancer risk was 1.44 times higher in mothers of multiples than in mothers

of singletons (95% CI 1.06–1.97). Risk was highest in women who gave birth to multiples from all embryos transferred (adjusted HR 1.86, 95% CI 1.01–3.43), and lower for those with multiples after incomplete embryo implantation (adjusted HR 1.31, 95% CI 0.76–2.25). *Conclusion:* A woman's potential to implant all transferred embryos may be associated with breast cancer risk. Further research is needed to confirm our results and to identify the underlying biological mechanisms.

MID-PREGNANCY, PERINATAL AND NEONATAL REPRODUCTIVE ENDOCRINOLOGY IN TWINS AND SINGLETON CONTROLS

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Introduction: The intra-uterine environment is considered a possible starting point for development of diseases later in life. This phenomenon is even more important when considering a twin pregnancy as these children are part of the intra-uterine milieu affecting their co-twin. We aimed to shed light on the question whether reproductive hormonal profiles in mothers and children differ in the case of a twin pregnancy compared to a singleton pregnancy and whether girls influence their male co-twin and vice versa. We collected data on an array of reproductive hormones in singletons and twins, and aimed to answer two main questions. (1) Are reproductive hormone profiles, in particular estrogens, androgens and progesterone, in mothers and babies different in case of a twin pregnancy compared to a singleton pregnancy? (2) Are reproductive endocrine profiles of girls (fetuses and newborns) influenced by their male co-twin and vice versa? *Materials and Methods:* We measured estrogens (estron [E1], estradiol [E2] and estriol [E3]), androgens (androstenedione (ADION), dehydroepiandrostenedione (DHEA) and testosterone (T)) using validated LC-MS/MS methods. Gonadotropins (follicle stimulating hormone (FSH) and luteinizing hormone (LH)), progesterone, anti-Mullerian hormone (AMH) and inhibin A and inhibin B were measured by commercial immunoassays. Hormonal profiles were compared between singletons and twins, between twins of the same and different sex, between different types of twins and between girls and boys. *Main Findings:* Estrogen and progesterone concentrations were higher in mothers of twins compared to singletons. However, twin babies had lower estrogen and progesterone concentrations at birth. Opposite-sex twin girls did not have higher androgens in cord blood compared to same-sex twin girls, but boys with a female co-twin had lower LH and inhibin B levels compared to same-sex dizygotic twin boys. So in opposite-sex twins we did not find distinct androgenic effects of boys on their female co-twin; however, twin boys show signs of impaired hypothalamic-pituitary-testicular activity. *Conclusion:* In contrast to current understanding, children from a twin are not overexposed to sex steroid hormones at time of birth despite higher concentrations in their mothers at time of delivery. Furthermore, the hypothalamic-pituitary-gonadal axis in twin children seems to be under central inhibition, particularly in boys with a sister as co-twin where there is impaired hypothalamic-pituitary-testicular activity in the boy. At time of birth an opposite-sex twin girl does not show androgenic influence from her co-twin.

THE GENETIC CONTRIBUTION TO THE ASSOCIATION BETWEEN NUMBER OF TEETH AND ARTERIAL SCLEROSIS

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Introduction: Recently, some researchers have reported the association between oral health and arterial sclerosis. They indicated retaining teeth was important to prevent lifestyle diseases such as arterial sclerosis. However, most of them ignored the genetic contribution to this relationship, although genetic factor would somewhat affect all kinds of diseases. Twin studies make it possible to investigate the genetic contribution to the relationship using quantitative genetic analysis. The aim of this study was to estimate genetic interaction on both oral health and arterial sclerosis using elderly twin participants. *Materials and Methods:* The Osaka University Center for Twin Research has conducted a survey of elderly twins from all over the country. Medical and dental examinations were performed individually. Carotid intima-media thickness (IMT) was measured as an indicator of arterial sclerosis. We considered the participants whose IMT were over 1.0mm as affected. The calibrated clinical dentists examined the number of remaining teeth from the orthopantomography. To assess the correlation between oral health and arterial sclerosis, a generalized estimation equation (GEE) analysis was conducted. After this analysis, co-twin control analysis was conducted only for the monozygotic discordant twins. Finally, we compared the difference scores of both IMT and number of teeth with regression analysis for monozygotic twins. In this analysis, genetic factors can be completely eliminated. *Results:* There were 90 monozygotic and 24 dizygotic twin pairs, with a mean age of 66.5 years. Number of teeth was negatively associated with arterial sclerosis with GEE analysis. The odds ratio of total number of remaining teeth (unit: 5 teeth) was 0.75. There were 18 individuals affected by arterial sclerosis in all the participants. Only four pairs were concordant and ten were discordant monozygotic twins. In the discordant monozygotic twins, there was no significant association between all the measurements of oral health and arterial sclerosis by co-twin control analysis. But, the estimate of odds ratio (0.75) is close to that of GEE analysis. Besides, the final regression analysis with difference scores showed a significant association between the number of teeth and arterial sclerosis ($p = .03$). *Conclusion:* From the first GEE analysis, it would be possible to say there was a significant association of tooth loss with arterial sclerosis. Because of the small sample size, there was not a significant association with co-twin analysis. But, considering the estimate of odds ratio and the result of the final analysis, we suggest the genetic factor would not strongly affect on both tooth loss and arterial sclerosis. In other words, tooth loss would be one of the strong environmental factors affect on arterial sclerosis.

HERITABILITY OF TEETH WITH DANISH TWIN REGISTRY

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Introduction: Generally, people loose their teeth at a later stage of life because of the direct causation of periodontal disease and dental caries. However, it is also true that there are some elderly people who retain more than 20 teeth. Tooth loss strongly relates to some chronic systemic diseases such as cardiovascular diseases, diabetes, and heart disease. To prevent the loss of teeth, it is valuable to

investigate what makes a difference in retaining teeth in the later stage of life. Twin studies make it possible to detect the genetic and environmental contribution to human traits. The aim of this study was to clarify the heritability and environmental influence of the number of teeth in two large population-based twin cohorts. *Materials and Methods:* The Danish twin registry is one of the largest registries in the world containing multiple births, and it is the oldest nationwide twin register. In this study, two cohorts were used: one was middle-aged Danish twins (MADTs) collected in 2001 from each of the consecutive birth years (1931 through 1952) and the other was the Longitudinal Study of Aging Danish Twins (LSADTs) collected in 1998 from each of the consecutive birth years (1931 through 1952). Among 5,396 Danish middle-aged and elderly twins in large cohorts, we collected the data of number of teeth as a categorical variable in later stage of life. The data was based on self-reported questionnaire. The data of teeth were divided two kinds of dichotomous variables, one is separated into all teeth or not, and the other is separated into no teeth or not. By case-wise concordance analysis, we examined the heritable association of good teeth and also of bad teeth using statistical software, R (mets package). *Results:* There were 2,309 monozygotic twins (male: 1,123, female: 1,186) and 2,960 same sex dizygotic twins (male: 1,421, female: 1,539) in our study. As for the distribution of number of teeth, 39.9% of all LSADTs, and 8.6% of MADTs were no teeth, 22.1% of all LSADTs and 45.1% of MADTs were more than 20 teeth remained. Overall, the polygenic ACE model gave the best fit to data with estimated heritability of 10% (95%CI: 0–40%) and common environmental contribution of 47% (22–72%) for loosing all teeth. The relative recurrence risk was 1.05 in MZ pairs and 1.04 in DZ pairs. For having all teeth, heritability was estimated at 40% (32–48%) from an AE model with relative recurrence risk of 1.04 in MZ and 1.02 in DZ pairs. As for the edentate, the case-wise concordance ratio of both monozygotic and dizygotic twins was so close along the age. But concerning excellent teeth, the case-wise concordance ratio was not close between monozygotic and dizygotic twins. *Conclusion:* We concluded that the difference between having excellent teeth and fine teeth is biological, but losing teeth is socially determined.

TWIN PREGNANCY: MATERNAL AGE RELATED COMPLICATIONS

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Introduction: To evaluate the relationships between maternal age and pregnancy complications as well as perinatal and obstetrics outcomes in women with twin pregnancy, and to find the cut-off level to define a higher risk for those complications. *Materials and Methods:* In total, 197 women with twin pregnancy, 82.7% (163/197) dichorionic-diamniotic and 17.3% (34/197) monochorionic-diamniotic, were analyzed. Clinical records were reviewed. Rates of pregnancy-induced-hypertension (PIH), preeclampsia (early and late-onset, mild and severe), gestational diabetes (on diet and under insulin therapy), mild carbohydrate intolerance (abnormal O'Sullivan's test), preterm labor (classified according gestational age), cesarean section (elective and emergency) and low birthweight (<1500 g and <2500 g) were evaluated. Spearman's correlation coefficient and ROC curves were used to analyze correlations with maternal age and to find the best cut-off level. *Results:* Maternal age was significantly positively associated with the rate of pregnancy-induced hypertension, severe preeclampsia, mild carbohydrate intolerance and elective cesarean section. On the contrary, it was significantly but negatively associated to the rate of preterm labor, specifically under 32 weeks of pregnancy. ROC curves demonstrated that the best cut-off level for pregnancy complications was 35 years. *Conclusion:* Pregnancy complications in women with twin pregnancy increases with maternal age and the best cut-off level to determine a higher risk is 35 years.

A GENOME-WIDE ASSOCIATION STUDY ON HALLUX VALGUS ANGLE (HVA) IDENTIFIES CANDIDATE LOCI: THE HEALTHY TWIN STUDY KOREA

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Introduction: Hallux valgus (HV) is one of the most common chronic structural foot deformities associated with genetic predisposition, age, sex, and footwear. Today, the growing tendency to reach an ideal appearance of female perfection explains the tacit social pressure to wear high heels, which may aggravate HV. Several studies have found that there is an association between constricting footwear and HV. Given the familial patterns of foot structure, several studies have been conducted to indicate how genetic factors play a role. However, specific genetic variants underlying HV have not yet been identified. The objective of this study was to investigate common genetic variants that confer susceptibility to the HV deviation in HV deformities through a genome-wide association (GWA) study. *Materials and Methods:* The Healthy Twin study is an ongoing cohort of adult same-sex twin pairs, aged ≥30 years, and their first-degree family members who have been recruited through participating hospitals since 2005. Among the 3,461 total, 1,265 individuals have had weight-bearing anteroposterior (AP) and lateral foot X-ray examinations. Out of those, 995 individuals (628 women) with genetic information (Affymetrix Genome-Wide Human SNP Array 6.0) were finally included for the GWA study. Hallux valgus angle (HVA) was obtained from each foot X-ray, and information about narrow-toed and/or high-heeled shoe use was collected through self-reported surveys. The software Merlin, an available approach for monozygotic (MZ) twins that included family-based data, was performed to interrogate the association between the trait of interest and genetic variants. *Results:* Potential candidate loci at 16p12.3 (p = 4.98E-07), 7q21.3 (p = 5.86E-07), and 1p13.3 (p = 1.80E-06) were identified. These regions were shown to comprise genes associated with diseases whose symptoms include phalangeal syndactyly, restricted joint mobility, joint stiffness, glycogen breakdown within muscles, and calcium accumulation in the elastic fiber tissue, which may be potential targets for HV treatment and general foot development. *Conclusion:* This study successfully identified potential genetic loci influencing HVA deviation, of which functions are of potential interest in foot development. These findings open up the need for further validation through replication studies, although it is challenging due to the lack of compatible measurements in other studies. It is expected it will guide future studies for exploring the interactions between genetic factors and environmental factors, and as a result, for foot health.

PERINATAL OUTCOMES OF SELECTIVE IUGR AND NON-SELECTIVE IUGR IN TWIN PREGNANCY

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Introduction: The aim of present study was to evaluate the perinatal outcomes of selective IUGR and non-selective IUGR in twin pregnancy. *Materials and Methods:* This was a retrospective study of

twin pregnancies from 2007 to 2014. A total number of 350 pairs of twins born between 2007 and 2014 at Ajou University Hospital were enrolled in the study. According to their birth weight, the 350 pairs of twins were divided into selective IUGR (sIUGR), non-selective IUGR (non-sIUGR), and normal growth group. Adverse perinatal outcomes were compared between three groups. *Results:* Among the 350 twin pregnancies, 70 (20%) were sIUGR, 14 (4%) were non-sIUGR, and 266 (76%) were normal growth group. There was no significant difference between IUGR and sIUGR according to chorionicity ($p = .620$). Vaginal delivery was significantly higher inthe non-sIUGR group compared to the sIUGR and normal growth groups (50% vs. 17% vs. 15%, $p = .003$). The incidence of fetal distress, chorioamnionitis, and discordance were higher in the non-sIUGR group than in the sIUGR and normal growth groups (fetal distress: 21% vs. 2.8% vs. 1.5%, $p < .001$, chorioamnionitis: 57% vs. 34% vs. 23%, $p = .003$, discordance 75% vs. 65% vs. 14%, $p < .001$). Maternal preeclampsia was higher in the IUGR groups (non-sIUGR and sIUGR) than in the normal growth group (28% vs. 21% vs. 9.0%, $p = .003$). With respect to perinatal outcomes, perinatal death was higher in the sIUGR group than in normal and non-sIUGR groups (17% vs. 7% vs. 6.6%) The incidence of poor perinatal outcome (any of the followings : NEC, BPD, RDS, and brain hemorrhage) was higher in both non-sIUGR and s-IUGR groups than in the normal growth group (25% vs. 19.3% vs. 11.7%, $p = .015$). *Conclusion:* There was significant difference between the sIUGR and non-sIUGR groups in terms of vaginal delivery, presence of fetal distress, chorioamnionitis, and presence of discordance. Poor perinatal outcome was higher in both non-sIUGR and sIUGR group compare to normal growth group.

THE INFLUENCES OF GENETIC AND ENVIRONMENTAL FACTORS ON SLEEP QUALITY

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Introduction: During the past 2 decades evidence has emerged that poor sleep quality has adverse health effects, which may be due to both genetic and environmental factors. Previous twin studies have highlighted the importance of genes to several subjectively defined aspects of sleep, including overall subjective sleep quality. Furthermore, population-based studies have shown that regular exercise improves sleep quality. The aim of the present study was to estimate the relative importance of genetic and environmental factors on sleep quality. *Materials and Methods:* Participants (1,022 twin singletons, 449 MZ and 573 DZ) aged 28–78 years were recruited from the Danish GEMINAKAR twin cohort, a longitudinal study initiated in 1997–2000. During 2010–2012, participants were followed up. Sleep quality was examined using a validated questionnaire, the Pittsburgh Sleep Quality Index. All covariates were assessed using a questionnaire on lifestyle and health. *Results:* The median (25th–75th percentiles) sleep quality score was 3 (2–5), indicating a good sleep quality, with no significant difference between MZ and DZ participants ($p = .734$). The phenotypic correlation coefficients were 0.39 and 0.12 for MZ and DZ pairs, respectively, indicating non-additive genetic effects. Our estimates revealed that sleep quality was highly influenced by non-shared environmental factors (0.66, 95% CI: 0.54–0.78) and more limited by non-additive genetic factors (0.34, 95% CI: 0.22–0.46) adjusted for leisure time physical activity, age, sex, smoking status, education level and the WHO-5. We found no evidence of influence by additive genetic factors. *Conclusion:* This study surprisingly indicates that neither the additive genetic nor the common environmental components influence sleep quality. The estimated contribution from non-shared environmental component suggests that promoting healthy lifestyles may improve sleep quality.

TWIN STUDY OF GENETIC AND ENVIRONMENTAL INFLUENCES ON INSULIN RESISTANCE

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Introduction: The prevalence of insulin resistance and type 2 diabetes has increased in past decades. Genetic and epidemiological studies have reported that insulin resistance is, at least in part, genetically determined. Moreover, a variety of environmental factors (e.g., poor sleep quality) have been suggested to be risk factors for the development and exacerbation of insulin resistance, whereas others (e.g., regular exercise) may reduce insulin resistance. The present study aimed to estimate the relative importance of genetic and environmental factors on insulin resistance. *Materials and Methods:* The study was based on the Danish GEMINAKAR twin cohort originally recruited in 1997–2000 and followed up in 2010–2012. A total of 954 twin singletons (411 MZ and 543 DZ) aged 28–76 years participated. Insulin resistance was estimated from the validated homeostatic model assessment (HOMA-IR) index. *Results:* The median [25th–75th percentiles] insulin resistance was 1.3 [0.9–1.9], with no significant difference between MZ and DZ participants ($p = .877$). The phenotypic correlation coefficient was 0.30 and 0.22 for MZ and DZ pairs, respectively, indicating additive genetic effects. Our estimates revealed that a high proportion of non-shared environmental factors (0.75, 95% CI: 0.62–0.87) and limited additive genetic factors (0.25, 95% CI: 0.13–0.38) contribute to insulin resistance adjusted for sleep quality, leisure time physical activity, age, gender, cholesterol, triglyceride, waist circumstance, BMI and fat mass. We found no evidence of influence of common environmental effects. *Conclusion:* In accordance with the literature we found that insulin resistance was highly influenced by non-shared environmental factors, suggesting that promoting healthy lifestyles may reduce insulin resistance. Furthermore, we found a minor additive genetic influence on insulin resistance.

DIFFERENTIALS IN NUTRITIONAL STATUS AND FEEDING PRACTICES OF UNDER FIVE TWINS IN NIGERIA

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Introduction: Adequate nutrition through appropriate feeding during infancy and early childhood is fundamental to the development of each child's full human potential. Nigeria has one of the highest twinning rate in the world; hence there is a substantial population of the under-5 twins. Several studies have been done on the IYCF and nutritional status of under-5 children in Nigeria; despite this, few

have focused on twins The objective of this study was to assess the differentials in the feeding practices and nutritional status of twins and singletons below 5 years of age in Igbo ora, Oyo State, Nigeria. *Materials and Methods:* The study was carried out in Igbo ora, a community reported to record the highest prevalence of twinning in Nigeria. Eighty-two mothers of twins and eighty-three mothers of singletons were selected through snowball and systematic sampling techniques, respectively. Anthropometric measurements were conducted to assess the nutritional status, while a structured questionnaire was used to assess socio-economic characteristics and infant and young child feeding practices of the mothers. *Results:* It was observed that mothers with singletons were more likely to have appropriate feeding practices than mothers with twins. Early initiation of breastfeeding was practiced by 45% of mothers with singletons, while 42% of mothers with twins reported the practice. The rate of exclusive breastfeeding among mothers of singletons was 15.7% while it was 7.3% among mothers of twins. The majority of mothers of singletons and twins continued breastfeeding beyond 1 year (97.6% and 92.7%, respectively). Introduction of complementary foods before 6 months was observed among 34.9% and 58.5% of mothers with singletons and twins, respectively; 23% of singletons were fed a minimum acceptable diet while 30.4% of twins had a minimum acceptable diet. The prevalence of wasting, stunting and underweight among singletons was found to be 14.5%, 36.1% and 19.3%, respectively, while twins were found to have a higher prevalence: 25.6%, 45.1% and 39.6%, respectively. The twins were two times more likely to be wasted (OR = 2.04), stunted (OR = 1.45) and underweight (OR = 2.75) than singletons. No significant difference was observed between the nutritional status of the first and second twin ($p > .05$), but the second-born twin was found to be more malnourished than the first-born twin. *Conclusion:* Infant and young child feeding (IYCF) was more likely to be practiced by mothers of singletons than mothers of twins. Also in this study, twins were found to be two times more likely to be malnourished than the singletons. This high level of malnutrition could be attributed to inadequate IYCF practices by their mothers. An intervention to improve the feeding practice of mothers and nutritional status of twins is recommended.

CONCEPTION MODE: INFLUENCE ON FIRST TRIMESTER MATERNAL SERUM MARKERS FREE β- hCG AND PAPP-A USED FOR ANEUPLOIDY SCREENING IN TWIN PREGNANCIES

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Introduction: Non-invasive prenatal testing (NIPT) for aneuploidy using cell-free DNA in maternal plasma is revolutionizing prenatal screening and diagnosis. Since April 2014 in the Netherlands, NIPT is offered as part of national study protocol (trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing) to those women pregnant with a singleton with increased risk based on the first trimester combined test screening (maternal age, ultrasound nuchal translucency [NT] measurement and maternal serum markers free β-hCG and PAPP-A). For twins, the NIPT is not offered yet in the Netherlands. Optimizing screening performance of the combined test in twins thus remains of great importance. A possible covariable on serum marker distributions is conception mode, and in singletons, serum markers are being corrected for it. Since assisted reproductive techniques (ART) contribute greatly to twinning, we assessed the influence of conception mode on serum marker distributions. *Materials and Methods:* Data of twin pregnancies were extracted from the database of our tertial fetal medicine center. Euploid twin pregnancies were selected. Maternal free β-hCG and PAPP-A were measured between 9 and 14 weeks of gestational using the Delfia Xpress (PerkinElmer, Finland) and are expressed as the weight corrected multiple of the median (MoM values) compared to singleton pregnancies. *Results:* A total of 200 cases were included. The mean maternal age was 34.3 years. Maternal free β-hCG and PAPP-A were measured between 63 and 96 days of gestation (mean 81 days). Pregnancies conceived with ART (IVF + ICSI) versus naturally conceived pregnancies showed a higher weight-corrected MoM free β-hCG ($n = 59/n = 141$, 2.18 vs. 1.91, MWU $p = .06$) and a lower PAPP-A (2.02 vs. 2.16, MWU $p = .40$). Subdivided for chorionicity, dichorionic twins after ART demonstrated higher free β-hCG and lower PAPP-A MoMs, although not significantly. *Conclusion:* Evaluation of the first trimester combined test for aneuploidy screening did only found a tendency to be elevated for the weight-corrected MoM free β-hCG and a decrease for the PAPP-A in ART twins compared to naturally conceived twins, although not significantly. In singleton pregnancies, marker levels are already currently corrected for conception mode in the first trimester combined test; however, for twin pregnancies further research is advised.

THE HUNGARIAN TWIN REGISTRY: PRESENT AND FUTURE

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Introduction: The Hungarian twin registry was founded in 2007, which contributed to the current understanding on the background of several disorders and psychological attitudes. *Materials and Methods:* The voluntary registry is growing continously mainly thanks to the media influence and good feedbacks, consisting of 650 monozygotic and dizygotic twin pairs of all ages (www.ikrek.com). *Results:* Our aim is to extend the registry to a population-based one, which could be possible by arguments and discussions on a governmental level due to the strict Hungarian data protection law. Twins are motivated to participate, which happened in a recent online survey pilot study assessing the genetic influences on political ideologies, in which study almost 100 pairs volunteered in few days. *Conclusion:* The review will summarize current possibilities, challenges and future plans of the Hungarian twin registry.

THE NEUREGULIN SIGNALLING PATHWAY IN ADDICTIONS

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Introduction: Nicotine dependence (ND) is the key factor sustaining persistent smoking, and is associated with several neuropsychiatric disorders; for example, schizophrenia (SZ), depression and alcohol dependence. Twin and family studies suggest shared genetic vulnerability of addictions and neuropsychiatric co-morbidities; however, underlying pathways and mechanisms are mostly unknown. Our recent GWAS on smoking behavior detected an association of DSM-IV ND diagnosis and a neuregulin receptor ERBB4, providing novel evidence for the involvement of the neuregulin signalling pathway (NSP) in addictions. The association was supported by replication in an Australian sample. Further, ERBB4 resides on linkage loci for smoking quantity and regular smoking. In a behavioral mouse model, ErbB4 expression increased during nicotine exposure and withdrawal, and the NSP was shown to be essential in the anxiety effects of nicotine withdrawal. Our aim was to scrutinize the role of

NSP genes in various addictions. *Materials and Methods:* The study sample was ascertained from the Finnish Twin Cohort study consisting of 35,834 adult twins born in 1938–1957. Based on earlier data, twin pairs concordant for ever-smoking were identified and recruited along with their family members (mainly siblings) for the Nicotine Addiction Genetics Consortium study. A total of 747 families, including 2,193 subjects, were assessed by structured psychiatric interview, DNA sample collection and additional questionnaires, resulting in detailed phenotype profiles covering substance use, abuse and dependence. Our recent genome-wide association study included 914 dizygotic twin individuals, 138 monozygotic twin individuals and 62 siblings. In follow-up analyses, an additional 917 subjects were included. *Results:* In our ongoing follow-up analyses we are utilizing 2,031 subjects (from 744 families) and genotypes extracted from 1000G imputed genome-wide genotype data. We are targeting all the 10 genes involved in the neuregulin signalling pathway using common and rare variant, copy number variation, and linkage analyses. Our sample contains extended sibsips (192 families with at least 4 family members), is enriched for smoking as well as comorbid traits, and is thus advantageous in family-based association and linkage analyses. Our initial results support the involvement of at least four NSP genes (ERBB4, NRG1, NRG3, and BACE1) in ND. *Conclusion:* By using a twin family sample we have been able to provide novel evidence for the involvement of the NSP in ND. Three of the NSP genes (NRG1, NRG3, ERBB4) have previously been robustly associated with SZ; thus, our results further suggest the NSP as a plausible underlying mechanism for the comorbidity of ND and SZ. Our future studies aim to to decipher the role of NSP and downstream targets and pathways in various addictions.

COMING TO GRIPS WITH HERITABILITY

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Introduction: Mark Twain wrote that 'the difference between the almost-right word and the right word is the difference between the lightning bug and the lightning'. Like many words used by diverse biological disciplines (e.g., 'environment'), the word 'heritability' is found useful for different purposes by investigators with different goals. This impedes scientific communication, and creates confusion among those seeking to understand etiology. It may be useful to put forward the point of view of one of the confused. *Materials and Methods:* Heritabilityis a simple English construct, and in my Oxford English Dictionary (OED) it is defined as 'The quality of being heritable, i.e. capable of being inherited'. That implies a nominal, not a quantitative characteristic, and if asked, most laypersons would likely agree with the notion that a disease is either heritable or it is not. Quantitative geneticists employ the term quantitatively, implying to the uninitiated, including clinicians, epidemiologists, and molecular biologists, that any set of persons affected by the same condition can be divided into those that are and those that are not caused by heritable elements. That is a puzzlement, because homeostasis is omnipresent and driven by genetic determinants. One can easily list known causes of disease (e.g., pathogenic organisms, toxic chemicals) that are not heritable, but it is more difficult to name diseases (including those caused by said pathogens and toxins) that are neither facilitated nor prevented by one or more genetic determinants. The effects of smoking are clearly mitigated/mediated by genetic determinants, as are the effects of exposure to phenylalanine, solar radiation and Mycobacterium leprae. Concurrent disease causes were nicely described by Brian MacMahon as converging threads in the 'web of causality' of one particular affliction in any given particular person, recognizing that the same manifestational entity can be produced by different causal webs. Of course, one can quantify the group impact of any exposure on a disease by quantifying the association between exposure and disease occurrence and computing a cause-specific attributable (absolute) risk, but the sum of all the genetic and environmental attributable risks is never unity but rises to infinity as knowledge grows. Since there is no finite sum of risks (no denominator), there can be no meaningful subfraction. *Results:* The 'heritability' fraction of which quantitative geneticists speak, of course, does not refer to the partitioning of any set of cases, but just provides a rough estimate of the degree to which heritable (vs. non-heritable) factors are responsible for the distribution of a given condition in a given setting at a given time. Of course that setting-specific distribution of disease simultaneously reflects the local prevalence of all the other causes of that condition, including those whose actions are mitigated or facilitated by the various variable genetic determinants. *Conclusion:* Thus if 'heritability' is quantified (by whatever method), it is always incumbent to emphasize to the reader that: (1) the same manifestation (i.e., condition) in different people is likely to be caused by different gene/environment combinations, (2)the fraction estimated is NOT a biologic characteristic of the disease, (3) the estimate can NOT be presumed generalizable to other settings or other periods, and (4) the measured 'heritable' fraction does NOT represent the fraction of disease that is immutable and ineligible for prevention.

DIVERSITY OF LEISURE-TIME SPORT ACTIVITIES IN ADOLESCENCE AS A PREDICTOR OF LEISURE TIME PHYSICAL ACTIVITY IN ADULTHOOD: A FINNISH TWIN STUDY

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Introduction: As many of the previous studies considering physical activity have concentrated on tracking from adolescence to adulthood, showing low to moderate positive correlation at best, we wanted to find out how diversity of sports in adolescence predicts the level of leisure-time physical activity in adulthood. Earlier studies suggest that participation in several adolescent physical activities simultaneously was moderately related to physical activity level in young adulthood. *Materials and Methods:* The study sample was drawn from the FinnTwin16 study cohort consisting of Finnish twins born in 1975–77. The participants were first surveyed at the age of 16 and then at the ages of 17, 18.5, 22–25, and 35. Information about the sport activities in adolescence was collected with a questionnaire considering exercise frequency, team sports, competitive action and a multiple choice question of 18 different sports. For the analyses, the number of different sport activities was pooled together into four categories. Physical activity level of a 35-year-old was calculated as leisure-time Metabolic Equivalent of Time (ltMET) (h/day) based on questions considering leisure-time exercise duration, frequency, intensity and active commuting. The distribution of ltMET not being normal, we chose a statistical approach to categorize participants into four activity classes (about 25% of participants in each category). In the multinomial logistic regression analysis we used the categorized amounts of adolescents' different sport activities to predict the participant's placement in the different activity classes in adulthood. Because the twins were sampled as clusters, the primary unit being the twin pair, the clustering of correlated observations from twin pairs was controlled for when computing standard errors of the coefficients using robust estimators of variance. The models adjusted with multiple confounders

were separately conducted for men (N = 1,491) and women (N = 2,057). The conditional logistic regression analysis was run for the 125 twin pairs (including 29 monozygotic pairs), that were extremely discordant. *Results:* Among men there was no significant association between diversity of sport activities in adolescence and ltMET in adulthood after adjustments. Interestingly, for women such diversity of participated sport activities in adolescence significantly predicted placement in a more active ltMET class in adulthood compared to the least active class. Odds ratios (OR) for the placement in the most active versus the least active class having 2–3, 4–5 and 6 or more participated sport activities (reference = one activity only) in adolescence were following: OR = 1.51 (p = .049), OR = 1.75 (p = .015), and OR = 2.28 (p = .004), respectively. However, the results were not replicated in the discordant pair analysis. *Conclusion:* From the results of multinomial logistic regression we can interpret that diversity of leisure-time sport activities in adolescence predicts greater leisure-time physical activity in adulthood in women. However, the discordant pair analysis suggests that this association may be confounded by familial factors.

THE NATURE OF THE RELATIONSHIP BETWEEN PRESCHOOL DRAWING AND SCHOOL MATHEMATICS: INSIGHTS FROM A LARGE TWIN STUDY

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Introduction: Drawing is a fundamental activity in preschool years and it is often considered as an index of children's emotional and developmental wellbeing. The relationship between drawing and cognitive development has been the subject of scientific investigations for more than a century. It is possible that, apart from reflecting general cognitive development, early human figure drawing can serve as a marker for mathematically relevant development. For example, awareness of number of body features, proportionality, appropriate use of space and symmetry may all be specifically related to mathematical development. This study examined the genetic and environmental etiology of individual differences in early drawing ability and of its longitudinal relationship with school mathematics. Additionally, using monozygotic twin (MZ) difference design, we explored the possible impact of one non-shared environmental influence, parenting, on drawing development. *Materials and Methods:* Participants were members of the Twins Early Development Study (TEDS; N = 14,760). All families with live twin births born in England and Wales between 1994 and 1996 were contacted by the Office of National Statistics on behalf of the study and over 15,000 families participated at first contact. The twins were assessed for human figure drawing ability at age 4 and 4 ½, and for mathematical ability later in development at ages 7 and 12. Measures describing differential parent-child interaction (parental feeling and parent-child communication) were collected via parental self-reports when the twins were 4 years old. *Results:* Drawing ability was moderately stable (average r = .42) over a 6-month period from when the twins were 4 to 4½. Individual differences in drawing at age 4½ were influenced by genetic (.21), shared environmental (.3) and non-shared environmental (.49) factors. Early drawing ability was related to later (age 7 and 12) mathematical abilities (average r = .20) and this relationship was explained by genetic and shared environmental factors that also influenced early general intelligence. MZ twin differences in early parenting, and specifically in negative parental feeling and instructive communication between parent and child when the twins were 4 directly predicted differences in drawing ability both at 4 and 4½, but effect sizes were small (R^2= .03). *Conclusion:* This study represents a step forward in our understanding of early drawing ability, how it develops and how it relates etiologically to other aspects of cognition and learning. Individual differences in drawing and mathematics were largely independent etiologically. To the extent that their etiology overlapped, that was also shared with general cognitive ability. Differences in parenting were found to have a very minimal impact on MZ differences in early drawing ability.

20 YEARS OF STUDYING MELANOMA RISK FACTORS IN QUEENSLAND TWINS

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Introduction: Risk of melanoma runs in families and we have conducted a large, longitudinal twin study of melanoma risk factors, including moliness and pigmentation factors, to try and elucidate the genetic and environmental influences. *Materials and Methods:* Since 1992 we have measured melanoma risk factors in Brisbane twins aged 12 and then again at 14. Around 1,500 pairs have been studied, as well as near-age siblings and, for some purposes, their parents. All have been GWASd. *Results:* Latest variance components estimates for risk factors, as well as GWAS results, will be presented. *Conclusion:* After 20 years' research, a picture of the genetic and environmental pathways leading to melanoma is starting to emerge.

ASSOCIATION OF COPY NUMBER AT THE SALIVARY AMYLASE GENE AMY1 AND SERUM AMYLASE LEVELS WITH METABOLIC PROFILES

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Introduction: Copy number at the salivary amylase gene (AMY1) has been shown to be positively correlated with both amylase gene expression and serum enzyme levels, with low AMY1 copy number showing strong association with increased body mass index (BMI) and risk of obesity (Falchi et al., 2014). These findings suggest that salivary amylase copy number may play a significant role in human adiposity and metabolism. *Materials and Methods:* Both AMY1 copy number and metabolomics data were measured in two cohorts including 1,479 women from the TwinsUK cohort. Moreover, serum salivary amylase levels, pancreatic serum amylase levels, and total serum amylase levels were measured in 219 female twins from the TwinsUK cohort. Metabolomics data have been generated through mass spectrometry in the TwinsUK cohort for fasting serum and plasma. Association studies of AMY1 genomic copy numbers and serum total, pancreatic, and salivary amylase levels with metabolomics data were performed independently using linear mixed models (including a random effect for zygosity and family structure for the TwinsUK cohort). AMY1 copy number was tested as both a continuous trait (all individuals) and a binary trait (individuals with high copy number [greater than 9 copies of AMY1] and low [less than 4 copies of AMY1]). *Results:* Salivary amylase levels in the TwinUK cohort were shown to be highly heritable (h2

= 0.81), and showed significant positive correlation with AMY1 copy number (R2 = 0.32; $p < 2.2 \times 10–16$). Negative association between salivary amylase and each of BMI (β = -0.062; $p = 4.15 \times 10$-3) and fasting insulin levels (β = -0.08; $p = .02$) was also observed. Various different metabolites were found to be associated with each of AMY1 copy number and serum enzyme levels. Notably, two metabolites, propionylcarnitine and succinylcarnitine, were negatively associated with serum amylase levels (min $p = 5.0 \times 10$-3 and $p = 1.0 \times 10$-3, respectively). Levels of the metabolite succinylcarnitine, which is a transport form of the free fatty acid succinate belonging to the butanoate pathway, has been previously positively associated with BMI in the TwinsUK and KORA cohorts (Suhre et al., Nature, 2011). Furthermore, 2-hydroxypalmitate metabolite, which is a biomarker of the activity of HAOX2 and plays a role in the general mechanism of fatty acid alpha-oxidation (Jones et al., J Biol Chem. 2000), was the strongest AMY1 copy number association observed in the TwinsUK cohort (β = 0.599; $p = 5.49$e-5). *Conclusion:* We have observed significant differences in metabolites involved in lipid, carbohydrate and amino acid metabolism associated with AMY1 copy number and serum amylase levels. Further investigation of the metabolic changes associated with low AMY1 copy number and amylase enzyme levels may enable us to better understand their association with BMI and increased risk of obesity. The study is currently being expanded through measurement of serum amylase levels in a further 6,000 subjects from the UK TwinsUK cohort and in over 2,000 subjects from the French DESIR cohort.

MANAGEMENT OF TWIN PREGNANCIES WITH BULGING MEMBRANES BY RESCUE CERCLAGE AFTER THE EXCLUSION OF INTRAAMNIOTIC INFLAMMATION AND SUBCLINICAL CHORIOAMNIONITIS

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Introduction: Rescue cerclage may be considered a treatment option for patients with twin pregnancies and a dilated cervix in the second trimester, since it associates favorable outcomes such as a high likelihood of delivery at >32 weeks and a high likelihood of survival. The aim of this study was to evaluate the pregnancy outcome of patients with twin pregnancies and bulging membranes treated by rescue cerclage after the exclusion of intraamniotic inflammation. This was ruled out by performing an amniocentesis of the first twin and determining an IL-6 levels below 2.9 ng/ml. Subclinical chorioamnionitis was also ruled out by studying the amniotic fluid the glucose, leukocyte and leukocyte esterase levels. Intraamniotic infection was excluded by performing cultures of amniotic fluid. *Materials and Methods:* Cohort study with all pregnant women with twin pregnancies and bulging membranes who were admitted into our hospital between January 2012 and June 2014. Patients underwent an amniocentesis of the first twin to quantify glucose, leukocytes, IL-6 and leukocyte esterase levels. Microbiological culture of the amniotic fluid was also done. All patients without intraamniotic inflammation or subclinical chorioamnionitis underwent a rescue cerclage. Those who did not accomplish these criteria were treated with intravenous antibyotic. *Results:* Will be shown in a flowchart. *Conclusion:* The exclusion of intraamniotic inflammation and subclinical chorioamnionitis in twin pregnancies with bulging membranes is associated with a higher gestational age at delivery. To perform a rescue cerclage may allow the improvement of both the pregnancy outcome and the comfort of the patient, since she can avoid bed rest. These are preliminary results of a larger study.

MATERNAL AND FETAL OUTCOMES IN TWIN PREGNANCIES OBTAINED FROM OOCYTE DONATION

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Introduction: The number of pregnancies obtained through oocyte donation (OD) is increasing, from 2.4% of all in vitro fertilization procedures in 2001 to 4% in 2009. Some studies have highlighted how OD pregnancies have a significantly increased risk of obstetric complications (pre-eclampsia, pregnancy-induced hypertension, fetal growth restriction, gestational diabetes, preterm premature rupture of membranes, post-partum hemorrhage, placental anomalies and cesarean sections) compared to pregnancies obtained from spontaneous conceptions. All the studies, however, comprised both single and twin pregnancies. This study analyzes the maternal and fetal outcomes of OD twin pregnancies delivered at the Gynaecological and Obstetrical Sant'Anna Hospital, Turin in a 5-year period. *Materials and Methods:* One hundred and four OD pregnancies were delivered between April 2008 and December 2013. The outcome of these pregnancies was compared with that of a control group of 146 spontaneously conceived twin pregnancies delivered during the same period. In both groups, we evaluated maternal characteristics (ethnicity, age, parity and BMI), the rate of obstetric complications and neonatal outcomes. We calculated the odds ratio (OR) and 95% confidence interval (CI) for all the maternal and fetal outcomes. *Results:* OD pregnancies are significantly associated with risk of pre-eclampsia (OR = 4.9 [2.5–9.8]), cesarean section (OR = 9.9 [2.9–33.5]), post-partum hemorrhage (OR = 4.3 [2–9,1]), maternal intensive care support (OR = 28.3 [3.7–216.6]) and pre-term delivery (OR = 1.9 [1.09–3.5]). We also found a higher risk of perinatal outcomes (low birth weight, very low birth weight and neonatal intensive care support) in OD pregnancies, but these results were not statistically significant. *Conclusion:* OD twin pregnancies are at higher risk of maternal complications than those spontaneously conceived. Since twin pregnancies in general are at higher risk, they receive special prenatal and perinatal care. Our data suggest that OD twin pregnancies need even more intensive care.

THE HERITABILITY OF CORONARY ATHEROSCLEROTIC PLAQUE BURDEN: A CLASSICAL TWIN STUDY

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Introduction: Twin studies provide a unique method for assessing the phenotypic impacts of environmental and genetic factors through the comparison of monozygotic (MZ) and dizygotic (DZ) twins. The heritability of coronary plaque morphology was not yet studied. Here we report our initial experience. *Materials and Methods:* In this classical twin study we plan to enroll 100 asymptomatic, adult twin pairs with no history of coronary artery disease. The percentage plaque burden, plaque volume and non-calcified plaque volume were assessed by coronary CT angiography (Philips 256-slice iCT, Best, The Netherlands). Plaque analysis was perfomed with a dedicated software (QAngio CT Research Edition, Medis B.V., Leiden, The Netherlands). The concordance between the MZ and DZ twins was detemined by using Spearman correlation, rMZ and rDZ

respectively. *Results:* At this point, 30 twins (mean age 57 ± 9years, 22% male), 6 MZ and 9 DZ pairs, were enrolled. Dyslipidemia was present in 57%, hypertension in 27%, diabetes in 10% of the twins and 33% of the twins were smokers. Coronary artery disease was present in 12 subjects and 56 plaques were detected. We observed a median total plaque burden of 40.3% (IQR34.7–45.9) with a concordance of rMZ: 0.80 and rDZ: 0.42; plaque volume of 39.6 (IQR:24.9–82.9) mm3, concordance of rMZ: 0,70 and rDZ: 0.70; non-calcified plaque volume of 15.4 (IQR:8.6-30.2) mm3, concordance of rMZ: 0.77 and rDZ: 0.72. *Conclusion:* Our first impression is that CCTA of twins provides a valuable tool to assess heritability of coronary plaque morphology. To perform a statistically robust analysis the enrolment of 100 twin pairs is warranted.

UNRAVELING THE GENETIC OF ALCOHOL DEPENDENCE: HERITABILITY ESTIMATES AND GWAS BASED ON THE AUDIT MEASURE

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Introduction: Alcohol dependence (AD) is among the most common and costly public health problems throughout the world contributing to morbidity and mortality. Twin, family, and adoption studies have shown that AD is moderately heritable but so far few known genes that moderate vulnerability to AD have been identified. These challenges underscore the importance of clarifying the etiology of AD as a key public health priority. *Materials and Methods:* The presence of Alcohol Dependence was ascertained in two longitudinal cohorts of the Netherlands Twin Register (NTR) and of the Netherlands Study of Depression and Anxiety (NESDA) by using the Alcohol Use Disorders Identification Test (AUDIT) to identify persons whose alcohol consumption has become hazardous or harmful. The heritability of AD was investigated through genetic structural equation modeling of data collected in MZ and DZ twins (N = 7,694). A genome wide association study (GWAS) was performed for 7,842 subjects and a total of 6,464,174 SNPS were analyzed. The total variance in liability to AUDIT-assessed AD explained by the joint effect of all SNPs (SNP heritability, h2SNP) was estimated using genomic-relationship-matrix restricted maximum likelihood (GREML) analyses implemented in GCTA. *Results:* The heritability of AD is 38% (8–65%), while the influence of shared environmental factors contributed 22% (0–33%). The remaining variance of 40% (33–49%) is due to unique environmental factors. Our GWAS p-values showed no evidence of inflation (lambda = 1.01). No single variant achieved a genome wide significance level of $p < 5\times10\text{-}8$. Among the top hits we identified 4 regions (4q34.1, 2p16.1, 6q25.1, 7p14.1) containing three or more SNPs within less than 70 kb of each other that show association with AD. The strongest association was detected with rs55768019 ($p = 7.58\times10\text{-}7$, OR = 0.80) near HPGD on chromosome 4q34.1. Results from GREML analyses showed that common SNPs jointly capture 22% (p = .002 se = 0.008) of the heritability of AUDIT-assessed AD. *Conclusion:* This is the first GWAS of AD using the AUDIT measure. We found several suggestive SNPs associated with AD located in known candidate regions for AD. Our heritability estimates from twins confirmed the previous report. Furthermore, we showed that common SNPs significantly capture a substantial part of the heritability of AUDIT-assessed AD.

THE GENETIC LANDSCAPE OF TWINNING: A META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES FROM THE TWINNING GWAS CONSORTIUM

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Introduction: The purpose of the Twinning Gwas Consortium (TGC) is to conduct meta-analyses of genome-wide association study data to identify genetic polymorphisms associated with the 'twinning' trait. Knowledge of these genes may identify key mechanisms controlling ovarian function and can provide a greater understanding of female fertility and infertility, the most common reproductive disorder. *Materials and Methods:* We performed a meta-analysis of 35,651 GWA samples collected from seven large twin registries in Europe and Australia. Three traits were studied: being a dizygotic twin, being a mother of dizygotic twin and being a monozygotic twin. The control group consisted of unrelated non-twin subjects. Imputation and GWA analysis were performed according to a standardized protocol in each of the cohorts separately. The association results were quality controlled centrally. All imputations were based on the same reference panel (1000 genomes phase 1 integrated release version (3). All GWA analyses were based on dosage data and corrected for sex and population stratification by controlling for ancestry PCs. *Results:* Three meta-analyses are currently underway and expected to be completed shortly. For each of the traits we analyzed a total number of cases and controls as follow : 4,073 DZ versus 12,538 controls; 8,135 MZ versus 23,532 controls and 1,653 mothers of DZ versus 7,248 controls. We will report the results during the 15th Congress of the International Society of Twin Studies in Budapest, Hungary. *Conclusion:* This is the first meta-analysis for GWAS of DZ, mothers of DZ and MZ twins to reveal the genetic factors contributing to twinning.

RECURRENCE OF SEVERE PRE-ECLAMPSIA SIX WEEKS AFTER SPONTANEOUS TWIN DEMISE

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Introduction: Pre-eclampsia does not resolve until placental anti-angiogenic factors are removed, usually by delivery of placenta and fetus. Demise of one twin of a dichorionic pregnancy reduces the maternal burden of anti-angiogenic factors as evidenced by 9 previous case reports of temporary resolution of pre-eclampsia following spontaneous or iatrogenic single twin demise. Recurrent pre-eclampsia or fetal growth concerns typically prompt delivery 6 to 8 weeks after single twin death. *Materials and Methods:* A literature review focused on maternal and surviving twin outcomes after spontaneous or iatrogenic single twin death associated with severe pre-eclampsia. The stimulus to this literature review was a multigravid woman who had significant non-modifiable risk factors for pre-eclampsia with a dichorionic twin pregnancy at 21 weeks gestation who strongly desired conservative management of severe pre-eclampsia. We wished to assess the safety of this request, especially in view of the patient living 300 km from a tertiary obstetric hospital. *Results:* A 34-year-old multigravid woman at high risk of pre-eclampsia due to twin pregnancy, obesity and previous eclampsia developed severe pre-eclampsia and selective fetal growth restriction at 21 + 6/40 with dichorionic placentation. Pre-eclampsia improved following spontaneous single twin death at 23 + 5 weeks but recurred requiring delivery at 29 + 4 weeks. *Conclusion:* This

case report confirms the pattern of pre-eclampsia resolution after death of a single twin: blood pressure normalises within 1 or a few days, proteinuria resolves within a week, elevated trans-aminases and/or thrombocytopaenia resolve within a month. The case report also supports the hypothesis that involution of vascular villi and normalisation of anti-angiogenic factors may take 9 weeks following single fetal twin death. During this time, pre-eclampsia and fetal growth restriction risks remain elevated above that of a singleton pregnancy of the same gestation. The literature review provided information for the patient and her family about risk and reproductive options. The review also provided information for effective shared care between rural obstetric and academic perinatal care.

A LARGE SURVEY ON BEHAVIOR, LIFESTYLE AND SLEEP HABITS AMONG ITALIAN ADOLESCENT TWINS

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Introduction: Although several studies have estimated the relative contribution of genetic and environmental influences on adolescent sleep habits, behavior, health status and lifestyle, only a few studies have collected, from twins and their parents, such a wide variety of information simultaneously. The primary aims of this study were to evaluate the impact of genetic and shared and non-shared environmental influences on the main traits investigated, to explore the association between them, and to assess the extent to which genetic and environmental factors explain the observed association. In particular, we explored the relationship between sleep habits and BMI, and between behavioral traits and alcohol/tobacco consumption. To achieve these aims, we used the twin design. Using information from both the twins and their parents, we also focused on the correlation between the self-reported and parent-reported data, especially regarding adolescent behavior. *Materials and Methods:* The sample consisted of about 700 twins (284 monozygotic, 274 same-sex dizygotic and 220 unlike-sex dizygotic) aged 14 to 18 years and enrolled in the population-based Italian Twin Registry. Adolescents and their parents completed mailed questionnaires about twins' activities, their habits and their current or perinatal health status. In particular, we were interested in adolescents' risk behaviors (e.g., binge eating, binge drinking, tobacco consumption), family relationships and stressful life events. In addition, our test battery included the Rosenberg Self Esteem Scale (Rosenberg, 1965), the Satisfaction With Life Scale (Diener et al., 1985) and the Youth Self Report (Achenbach, 1991). We also administered the Child Behaviour Checklist (Achenbach, 1991) to get information about twins' behaviours from the parents. Finally, we collected information on the quality of sleep of the twins using the Pittsburgh Sleep Quality Index (Buysse, 1988) and the Short Insomnia Questionnaire (Violani et al, Brain Research Bulletin, 2004). *Results:* Preliminary results show that genetic factors substantially influence externalizing symptoms and alcohol consumption, and are the major contributors to the relation between these two phenotypes. Our results also suggest genetic and non-shared environmental effects on sleep duration, with no influence of shared environment. Some differences among age groups were detected. Twin correlations for symptoms of insomnia were higher in MZ compared to DZ twins, pointing to a genetic effect on this trait. *Conclusion:* The analysis of data collected in our large and well-characterised cohort of twins is ongoing, and final results on the genetic and environmental contributions to each of the traits investigated and to the association between them will be presented and discussed.

DOES BREASTFEEDING BEHAVIOR RUN IN FAMILIES? EVIDENCE FROM TWINS, THEIR SISTERS AND THEIR MOTHERS IN THE NETHERLANDS

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Introduction: Breastfeeding is suggested to relate to health benefits both in the mother and the child. Genetic effects may explain this association. However, the heritability of initiation of breastfeeding is widely unknown. Our aim was to study the prevalence of initiation and the heritability of breastfeeding in the Netherlands. *Materials and Methods:* The present study was carried out in 5,581 participants from the Netherlands Twin Register and included female twins, their sisters and mothers born between 1911–1991. Date of birth was recoded to four categories (born before 1955, 1955–1964, 1965–1974, 1975 or later). Breastfeeding was self-reported by the participants and its prevalence was estimated stratified for birth cohort. To estimate the heritability extended twin-family modeling was done with the SEM package OpenMx in R. *Results:* The prevalence of breastfeeding increased with more recent birth cohorts (68% of the oldest and 84% of the youngest participants had breastfed). Breastfeeding aggregated within families. Heritability of breastfeeding was 48%, while specific twin environment explained 30% and unshared environment 22% of the differences in initiation of breastfeeding. *Conclusion:* We conclude that women born later in the 20th century had higher probability to initiate breastfeeding. Both genetic and environmental factors affect the decision to initiate breastfeeding. This should be considered when promoting breastfeeding and helps us to understand the link between breastfeeding and health.

IS THERE GENETIC OVERLAP BETWEEN PERSONALITY, EXPECTANCIES AND SYMPTOMS OF CANNABIS USE DISORDERS?

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Introduction: Previous research showed that cannabis expectancies (i.e., cannabis can make you feel less shy or is a good way to have fun) totally or partially mediate the association between personality and cannabis outcomes. However, the etiology of their relationship is unknown. Although there is evidence of inheritance of personality and cannabis use disorders, to our knowledge, no previous studies have examined the heritability of cannabis expectancies, or in which measure there is genetic overlap between personality, expectancies and cannabis symptoms. *Materials and Methods:* The sample was composed by 856 same-sex twin pairs who had tried cannabis at least once in their life (mean age = 20.33 years; 53% females). They completed the MPQ, which assesses the personality dimensions of positive emotionality, negative emotionality and constraint; the expectancies questionnaire, which assesses social/fun expectancies, mood regulation expectancies and total positive expectancies; and an interview of substance use disorders, which was used to calculate the total number of lifetime DSM-III R cannabis abuse or dependence symptom criteria met. We utilized multivariate Cholesky decompositions to decompose the genetic and environmental covariance between personality, expectancies and cannabis use

disorder symptoms in men and women. *Results:* In both males and females, the highest phenotypic correlations were found between low constraint, social/fun expectancies, mood expectancies, total positive expectancies and cannabis symptoms. Personality (.36–.49) and cannabis symptoms (.38–.66) showed similar heritability indices to those found in previous studies. We also found moderate evidence of inheritance for social/fun expectancies (.31–.34) and positive expectancies (.32) in men. In women, heritability indices were lower (.09–.16), and the influence of shared environment (.21–.23) was also found for social/fun expectancies. The correlations between low constraint, expectancies and cannabis symptoms in men were due to genetics, while for women were due to genetics and nonshared environment. *Conclusion:* To our knowledge, this study is the first to examine the heritability of cannabis expectancies. We found significant but modest and low inheritance indices for cannabis expectancies in men and women respectively. In addition, different etiological pathways seem to account for the associations of personality, expectancies and cannabis symptoms between males and females.

FETAL REDUCTION IN MONOCHORIONIC MULTIPLE PREGNANCY

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Background: In past decades, the introduction of IVF into the daily practice of infertility treatment has resulted in 2 million newborn worldwide but has also led to a dramatic increase in the rate of multiple pregnancies. In ART treatment, not only the rate of multiple pregnancies increases but also the rate of monozygotic/monochorionic twins, and the rate of monozygotic/monochorionic pairs in high order multifetal pregnancies are increased as well. The rate of monochorionic twins, in combination with a singleton in triplets, and high order multiple pregnancies has significantly increased. These pregnancies have a high rate of complications, such as pregnancy loss and prematurity, as well as specific disorders such as twin reversed arterial perfusion (TRAP), twin-to-twin transfusion syndrome (TTTS) and selective intrauterine growth restriction (sIUGR). So, prenatal counseling and comprehensive discussion with the patient about the risks of both conservative and aggressive pregnancy management is an extremely important part of care in specialized perinatal centers. *Materials:* The data on fetal reduction (FR) during the first 6 years (1996–2001) was compared with data of FR during the last 6 years (2008–2013). *Results:* The number of patients who had FR procedures reduced almost two times from 258 to 137. That can be explained by the stricter embryo transfer policy in the past decade. From 234 triplets and high order in the first period, 220 patients had only singleton compounds (94%), and 14 had monochorionic pairs (6%). In the second period, the frequency of monochorionicity among triplets and high order (109) increased dramatically and reached 27–29% out of 109. In the past decade, embryo transfer at the blastocyst stage of development has become more common and this has quite possibly influenced the rate of monochorionicity. In all cases except one, the decision of perinatal counseling was that monochorionicity is an indication for reduction of the MC pair of fetuses. In one case, a monochorionic pair was declined from reduction due to the presence of a structural anomaly in the singleton fetus. The remaining pair developed sIUGR, and acute CS delivery was performed early in the third trimester. In most cases, multifetal reduction in monochorionic pairs is performed by a single insertion technique. In two cases of TRAPs, intathoracic injections to 'pump' fetuses were performed and that was enough to stop fetal circulation in both monochorionic fetuses. The monochorionic component in multifetal pregnancy reduction did not influence the short-term and long-term outcomes compared with results of reduction of the same number of dichorionic fetuses. *Conclusion:* Monochorionicity is a quite frequent complication of ART, especially in blastocyst embriotransfer technology. Monochorionicity is suggested as an indication for special counseling for FR.

TRAP-SYNDROME WITH SPECIFIC NEPHRO-ACARDIUS FORMATION

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Background: Despite twin reversed arterial perfusion (TRAP) syndrome being described there is lack of information about anatomy formation and pathophysiology of acardiac fetuses. A monochorionic diamniotic pregnancy (MCDA) complicated by TRAP with nephro-acardius polyuretic specific formation and postmortem anatomy structure evaluation is presented. *Case report:* A 30-year-old nulliparous with MCDA twins complicated with TRAP syndrome was referred to our clinic at 19 weeks gestation with normal Doppler PI blood flow in the ductus venosus (DV) in the pump twin and signs of polyhydramnion in the acardiacus amniotic sac. It was decided to choose a conservative management of the pregnancy with dynamic ultrasound and Doppler evaluation. Over the next 9 weeks, Doppler indices of blood flow were normal but the amniotic fluid volume progressively increased. At 28 weeks the patient was admitted due to clinical sign of polyhydramnios with maximum vertical pocket (MVP) of 110 mm. Amnioreduction and evacuation of 2100 ml of amniotic fluid from the TRAP fetus sac was performed. Karyotype of the TRAP fetus was normal — 46, XX. A pessary was placed due to a short cervix and for preterm labor prophylactic. Amnioreduction was repeated two more times at 31 1\7 and 34 2\7 weeks with evacuation of 3500 ml and 3000 ml of amniotic fluid respectively. At 35 5\7 weeks of pregnancy, a progressive increase of polyhydramnios (MVP — 150 mm), deterioration of umbilical arteries blood flow with irregular absent of end diastolic component, elevation of DV PI to 1.15 and slight tricuspid regurgitation as markers of the pump fetus heart failure development were detected. Cesarian section was performed; the pump twin's weight was 1970 g with an Apgar score of 7 at 1 minute and 7 at 5 minutes; the acardius twin weight was 1990 g. External examination of the TRAP fetus showed absence of fetal head and rudimental hair on the upper part of the body, both feet had 4 toes with an absence of small toes, and omphalocele with bowel loops was present. CT and MRI of the TRAP fetus additional to anatomic section were performed. Postmortem examination of the TRAP fetus showed the absence of cardia, lungs, spleen, liver, pancreas. The specific thing was that the acardiac fetus had a fully developed urinary system — two kidneys with direct conection with the main (aorta) vessel, two ureters, bladder and urethra. Perhaps this explains the specificity of polyhydramnios present in the acardiac twin amniotic cavity during pregnancy. *Conclusion:* Supplemental examination methods can provide additional information of the specific characteristics of acardiac twin anatomy

and explain some fetal-related specific complications during pregnancy.

METHODS FOR STUDYING HERITABILITY OF CANCER DIAGNOSIS USING TWINS

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Introduction: Different kinds of cancer are known to be quite heritable, although the extent to which variation in risk by age is explained by genetic factors remains uncertain. We addressed this question with respect to breast cancer by analyzing data on a large cohort of Nordic twins. *Materials and Methods:* We studied 21,055 monozygotic and 30,939 dizygotic same sex female twin pairs from the Nordic Twin Study of Cancer cohort, the largest in the world, consisting of data from the Danish, Finish, Norwegian and Swedish Twin registries. We incorporated time-to-event analyses to estimate the concordance risk and heritability accounting for right-censoring due to individuals still alive or lost to follow-up and competing risks of death, essential sources of biases that have not been accounted for before. We therefore extended the approach used by Lichtenstein et al. (NEJM, 2000). We estimated the cumulative incidence using the non-parametric Aalen-Johansen estimator and taking account for left-censoring due to variable initiation of cancer registration. We determined the casewise concordance in MZ and DZ twins and its dependency on the age at diagnosis, weighting the sample by use of the additive Aalen model and the Kaplan-Meier method to handle censoring. Moreover, we estimated the cumulative heritability using a time-varying biometric ACE-model both on the liability and on the risk scale. *Results:* We found a lifetime incidence of breast cancer of 8.8% taking account of the censoring, compared to 3.6% in the simpler model ignoring censoring. The casewise concordance with censoring was estimated to be 0.24 in monozygotic and 0.18 in dizygotic twins, compared to 0.19 in monozygotic and 0.11 in dizygotic twins if we ignore censoring. We found heritability explains 24% of the variation while common environment explains 18%, both significantly higher than zero and different from the heritability of 38% and common environment of 7% one would get from the model ignoring censoring. We observed that the heritability is relatively stable over age while the common environment component slightly decreases. Moreover, we observed slightly higher heritability and lower common environment effects for pre-menopausal breast cancer compared to post-menopausal breast cancer. *Conclusion:* We found significant heritability and common environment effects in the liability for breast cancer in Nordic Twins. Furthermore, we demonstrated that ignoring the censoring and competing risk gives heavily biased and misleading results, substantiating the need for taking these factors into account.

TWIN PREGNANCY COMPLICATED BY THE INTRAUTERINE DEATH OF ONE TWIN. PROBLEMS AND PERINATAL OUTCOMES ACCORDING TO CHORIONICITY

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Introduction: Intrauterine death of one fetus in a multiple pregnancy is associated with significant morbidity and mortality in the newborn that survives. The objective of our study was to review the obstetric conditions and immediate perinatal outcomes of these pregnancies. *Materials and Methods:* A retrospective comparative study of twin pregnancies that had an intrauterine death of at least one of the fetuses was conducted, according to chorionicity, at our centre between January 2008 and December 2013. *Results:* We had 34 cases, 10 monochorial and 24 bichorial. 18 intrauterine deaths occurred in the 2nd trimester and 16 happened in the 3rd trimester. *Conclusion:* According to the literature, monochorial pregnancies have worse perinatal outcomes than bichorial pregnancies, and these differences are more manifest regarding chorioamnionitis and neonatal deaths. Early diagnosis of monochorial twins and subsequent ultrasounds have to identify a possible discrepancy in the weight and a possible feto-fetal transfusion syndrome, which caused the majority of fetal deaths in monochorial gestations in our cases. If we analyze both groups together, we can conclude that: A conservative treatment is a good option where there is not a risk for the surviving twin. We had only 4 cases of chorioamnionitis. The majority of our complications were due to prematurity. The incidence of premature delivery in our cases was elevated, but most of the cases were above 28 weeks. Cesarean section was the most common way of delivery, because of fetal presentation and obstetric emergencies, so we do not think that a cesarean would improve the prognosis of the surviving fetus.

ROLE OF A GLUCOCORTICOID BOOSTER AFTER THE ADMINISTRATION OF A COMPLETE COURSE WITH TWO DOSES FOR FETAL LUNG MATURATION IN TWIN PREGNANCIES

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Introduction: Preterm labour takes place in 7–10% of all deliveries, becoming the most important cause of perinatal morbidity and mortality in relation to an increase of the incidence of diseases such as respiratory distress syndrome, intraventricular haemorrhage, sepsis or necrotizing enterocolitis. Ligging and Howie described the efficacy of antenatal glucocorticoids in diminishing respiratory distress syndrome 30 years ago, its use undeniable nowadays in the management of pregnancies at risk of preterm labour. Currently, the incidence of twin gestations is increasing because of the rise in assisted reproduction technology. These gestations entail greater risk of preterm labour that results in a need to accelerate fetal lung maturity. Despite the widespread use of glucorticois in these pregnancies, there is no consensus either in the regimen of administration nor in their efficacy compared with single pregnancies. *Materials and Methods:* A retrospective clinical review was conducted to compare obstetric and perinatal outcomes between two groups of twin pregnancies at risk of preterm labour that have been attended in our hospital. We included all preterm twin pregnancies that were admitted in our centre in 2013. The group was split in two, one receiving a course of two doses of glucocorticois and the other receiving a booster shot after the same course. In all patients intramuscular maternal betamethasone was used for accelerating fetal lung maturation. A statistical analysis was performed using X-squared and U-Mann-Whitney tests when appropriate. Differences were considered as significant if $p < .05$. *Results:* In our series, 18 twin

pregnancies were included for final analysis, 9 in each of the two groups. No differences were found in maternal age nor gestational age at the time of finalizing gestation between the two groups. With respect to perinatal outcomes, no statistically significant differences were seen in biophysical parameters and other perinatal results as rate of admission to the neonatal intensive care unit or incidence of respiratory distress syndrome. *Conclusion:* We have not found an improvement in terms of perinatal and obstetric outcomes with the administration of a booster after a course of two doses of betamethasone for acceleration of lung maturity in twin pregnancies at risk of preterm labour. However, our results are limited by the sample size, it being necessary to use a bigger sample size to obtain more reliable results.

POSTTRAUMATIC STRESS DISORDER SYMPTOMS AND MIGRAINE HEADACHE: EXAMINING MODELS OF CO-OCCURRENCE WITH TWIN ANALYSES

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Introduction: Posttraumatic stress disorder (PTSD) is a major public health concern that affects about 9% of the general population and exhibits moderate heritability. A growing body of literature shows a consistent association between PTSD and migraine headache (MH) symptoms, the co-occurrence of which is associated with higher rates of disability. Despite this consistent association, the nature and mechanisms of the relationship are not well understood. Several theoretical models, focused on shared vulnerability, shared mechanisms, and causal dynamics have been proposed for the association of PTSD and pain that may apply to the link between PTSD and MH, with little scientific evidence to either support or refute any of these models. The specific aims of this study were to: (1) examine the extent to which shared genetic contributions convey a shared vulnerability to the association between PTSD and MH symptoms, and (2) use longitudinal twin data to estimate the direction of this relationship. *Materials and Methods:* Data from the University of Washington Twin Registry were used to address the aims of the study. The Impact of Events Scale and the Migraine Screen Questionnaire were used to measure PTSD and MH symptoms, respectively, at both the time of initial Registry Survey and at follow-up. Univariate and bivariate biometric modeling with data from 3,369 monozygotic (MZ) and dizygotic (DZ) pairs were used to address aim 1. Cross-lagged twin differences analyses with data from 1,134 MZ pairs at both time points were used to address aim 2. All analyses were conducted separately by sex due to documented sex differences in PTSD and MH. *Results:* PTSD and MH symptom scores were significantly higher in women compared to men, supporting our a priori decision to conduct sex-stratified analyses. A modest phenotypic association was found between PTSD and MH symptoms for women ($rp = .177$, $p < .001$) and men ($rp = .194$, $p < .001$). About 28% of the variance in PTSD symptoms was due to additive genetic influences in both men and women; 31% of the variance in MH symptoms in men was due to additive genetic influences, while 41% of the variance in MH symptoms in women was due to additive genetic influences. The proportion of the phenotypic association attributable to additive genetics that are common to both PTSD and MH symptoms was an estimated 38% in men and 68% in women. The cross-lagged MZ twin difference model did not find PTSD symptoms at Time 1 to be directly related to MH symptoms at Time 2, accounting for less than 1% of the variance in MH symptoms at Time 2 in both men and women. Similarly, MH symptoms at Time 1 predicted less than 1% of the variance in PTSD symptoms at Time 2 in both men and women. *Conclusion:* Findings from analyses to address both aims provide general support for a shared genetic vulnerability to PTSD and MH symptoms, rather than one condition directly influencing the other. Specifically, these findings suggest that there is a modest overlap in genetic influences common to both PTSD and MH symptoms in men and women, and that this overlap is potentially more substantial for women. Further exploration is needed of genetic, biological, physiological, psychological, and behavioral vulnerability factors underlying these conditions, and how they may differ by sex. Understanding the underlying mechanisms that link PTSD and MH symptoms can provide insight into the development of tailored psychological and pharmacological interventions.

HERITABILITY AND FAMILIAL RISK OF CANCER IN THE NORDIC TWIN COHORTS

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Introduction: Twin studies provide quantification of heritable factors and estimate familial risk in cancer by leveraging the unique genetic and familial relatedness of twins. We now update the Nordic Twin Study of Cancer (NorTwinCan) cohort with 15 years of additional follow-up and 3-fold more cancer cases than previously analyzed. *Materials and Methods:* The NorTwinCan cohort includes 133,689 monozygotic (MZ) and dizygotic (DZ) twin pairs from nationwide registries in Denmark, Finland, Norway and Sweden. We used time-to-event analyses to estimate the concordance risk and heritability (and 95% confidence intervals, CI) for 23 cancer sites, with complete follow-up through linkage with cancer and mortality registries. Statistical models accounted for censoring and competing risks of death. *Results:* During a median 40-year follow-up, 51,681 cancer cases were diagnosed. The heritability for prostate cancer was 58% (95% CI 52–63%), the highest of any malignancy. The absolute risk of prostate cancer in a twin given his cotwin also had prostate cancer (concordance risk) was 32% in MZ and 16% in DZ twins. For breast cancer among women, the heritability was 28% (95% CI 12–52%) and concordance risk 29% for MZ and 21% for DZ twins. There were notable differences in findings for colon and rectal cancer: the data supported a significant genetic component to colon (16%, 95% CI 2–63%) but not for rectal cancer. For testicular cancer, with a cumulative incidence of 0.4% in the population, the concordance risk was substantial among MZ (23%) and DZ (11%) twins, with heritability of 36% (95% CI 2–95%). Significant heritability was also present for cancers of the kidney (23%, 95% CI 11–42%), lung (25%, 95% CI 12–44%), melanoma (39%, 95% CI 8–81%), ovary (28%, 95% CI 15–47%), stomach (24%, 95% CI 5–65%), and uterus (24%, 95% CI 14–87%). *Conclusion:* Heritability estimates

are now more reliable and for some cancers higher than previously reported. For most cancer sites, many genetic determinants remain to be discovered in genome wide association studies.

PLACENTAL DISORDERS IN BICHORIONIC TWIN PREGNANCY IN RELATION TO CONCEPTION, SPONTANEOUS VERSUS HOMOLOGUE/HETEROLOGUE ASSISTED REPRODUCTION

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Introduction: The incidence of multiple pregnancies has risen significantly over several decades, primarily due to assisted reproductive technologies (ART). Compared with singleton pregnancies, twin pregnancies are at increased risk of virtually all obstetrical complications, including placental disorders such as hypertension, preeclampsia, fetal growth restriction and abnormal placental insertion. As well, conception by in vitro fertilization is associated with an increased incidence of several pregnancy-related complications. To our knowledge, there has been no work considering the risk of obstetrical adverse condition specifically in twin pregnancies in relation to the mode of conception. The purpose of this study was to assess the incidence of disorders secondary to placental dysfunction among twin pregnancies according to the conception, spontaneous versus assisted. *Materials and Methods:* We retrospectively reviewed our data regarding twin pregnancies followed in specialistic outpatients' clinic at IRCCS San Raffaele, Milan, from January 2008 to December 2013. Data collection included maternal age, mode of conception, medical history, gestational age at delivery, mode of delivery, birth weight, complication of pregnancy (specifically gestational hypertension, preeclampsia, intrauterine growth restriction and placenta previa). *Results:* A total of 266 women with bichorionic twin pregnancy were included in the study: 103 conceived spontaneously (S), 132 underwent homologue ART (HO-ART) and 31 heterologue ART (HE-ART). Mean maternal age in the S, HO-ART and HE-ART groups was different (S: 33.5 yrs; HO-ART: 35.6 yrs; HE-ART: 39.8 yrs). The mean gestational age (S: 36 weeks; HO-ART: 35.3 weeks; HE-ART: 34.2 weeks) at delivery and weight of the twins did not differ significantly in the three groups (S: 2423.5 g; HO-ART: 2306 g; HE-ART: 2190 g). The incidence of hypertensive disorders was significantly higher in the HE-ART group compared with the spontaneous and HO-ART groups (S: 12.6%; HO-ART: 11.4%; HE-ART: 32.3%; $p < .05$). To avoid bias due to different maternal age in the three groups (HE-ART older than S), we evaluated the incidence of hypertensive disorders, excluding patients younger than 37 years old: the results were similarly significant (S: 3.45%; HO-ART: 10.34%; HE-ART: 37.5%; $p < .05$). The incidence of intrauterine growth restriction was not statistically different among the three groups: it seems to us that twin pregnancy is the main risk factor for developing fetal growth restriction regardless of the conception. The incidence of placenta previa is higher in the ART group (5.2%) compared with the spontaneous group (1.8%); the difference is not statistically significant probably because there were only 10 cases of placenta previa. *Conclusion:* As more couples use ART and, recently, HE-ART, to conceive, subsequent maternal and neonatal risks need to be evaluated. HE-ART is associated with significant maternal complication and in particular should be considered as an independent risk factor for placental disorders in twin pregnancies. These considerations warrant attention and specific counseling when planning ART and during subsequent obstetrical assessment to guarantee adequate information to the couple and to optimize maternal and neonatal outcome.

EXTERNALIZING BEHAVIOR PROBLEMS IN ADOLESCENCE AND SICKNESS ABSENCE IN ADULTHOOD

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Introduction: Child and adolescent mental health problems have been shown to continue into adult years as well as have impact on adult socioeconomic outcomes, including sickness absence. Short- and long-term sickness absence due to mental diagnoses (e.g., depression) have continuously increased in several European countries during the past decades and especially among young adults. Previous studies of sickness absence have mainly focused on identifying psychosocial or occupational risk factors, while the impact of child and adolescent mental health on sickness absence has been less studied. The aim of the present study was to investigate whether externalizing behavior problems during child development increases risk for sickness absence in young adulthood. *Materials and Methods:* The study sample included 2,690 twins born 1985–1986 in Sweden who have participated in the Twin Study of CHild and Adolescent Development (TCHAD). The twins were followed repeatedly at ages of 8–9, 13–14, 16–17, and 19–20 years. Externalizing behavior problems during child development were evaluated by Child Behavior Checklist. Data on sickness absence were obtained from the Swedish National Social Insurance Agency for the years 2001–2010. Logistic regression analyses were applied to calculate odds ratios and the importance of familial factors was analyzed by applying conditional logistic regression models. *Results:* The prevalence of sickness absence during the follow-up was about 12% and 16% among males and females, respectively. Externalizing behavior problems measured in late childhood implied an increased risk for sickness absence in young adulthood (OR: 1.03 [1.01–1.04]). Also, behavior problems present during adolescence increased the risk for future sickness absence (13–14 years: OR: 1.03 [1.02–1.05]; 16–17 years: OR: 1.03 [1.01–1.04]; 19–20 years: OR: 1.02 [1.01–1.04]). The associations were not explained by familial factors. *Conclusion:* Sickness absence in young adulthood was significantly predicted by externalizing behavior problems measured in late childhood and adolescence. The results suggest that early implementation of programs supporting a successful start in working life may benefit children with externalizing behavior problems.

DISPOSITIONAL LIFE SATISFACTION AND DSM AXIS II PERSONALITY DISORDERS

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Introduction: The extent to which subjective wellbeing and psychopathology share etiological influences has been studied to a very limited degree. The few studies that are published to date have focused almost exclusively on anxiety and depression. This study examines the genetic and environmental influences on associations between dispositional life satisfaction (LS) and DSM-IV Axis II personality disorders (PD). *Materials and Methods:* We examined associations between dispositional life satisfaction (assessed twice, 6 years apart) and dimensional representations of DSM-IV Axis II personality disorders obtained by structured clinical interviews in a population-based sample of adult twins ($n = 2{,}801$) using stepwise logistic regression. Multivariate twin models were then fitted using the Mx program to estimate heritability (H^2) and genetic and environmental correlations. *Results:* Dispositional LS was significantly associated with dimensional representations of all 10 PDs, but uniquely associated with three PDs only, including Borderline

PD (r = -.41), Avoidant PD (r = -.37) and Paranoid PD (r = -.26). The phenotypic correlations were accounted for by both genetic and environmental influences. The overlap between etiological factors was moderate, and the genetic overlap (rg: -0.47 to -0.67) greater than that of the environmental factors (re: -.10 to -.040). The $H^2$of LS was estimated to be 0.72, and the $H^2$of Borderline, Avoidant and Paranoid PD to be 0.36, 0.35 and 0.20, respectively. *Conclusion:* Dispositional life satisfaction is uniquely and negatively associated with Paranoid PD from cluster A, Borderline PD from cluster B and Avoidant PD from cluster C. The etiological influences are partly overlapping, with the commonality of the genetic influences exceeding that of the environmental influences.

HISTORICAL TWINNING RATES IN NORWAY

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Introduction: It is well known that the twinning rate has increased considerably in the developed countries since the 1980s. It has also been noted that the twinning rate in the 1960s and 1970s was exceptionally low. In Norway, the twinning rate has increased from 1% in the period 1967–1987 to a maximum of 1.95% in 2002, and then later decreasing to 1.6% in 2012. In large part these changes can be explained by first the introduction of, and then improvements in artificial reproductive technologies (ART). The aim of the current study is to perform detailed analyses of Norwegian twinning rates for the period 1826 to 2012. *Materials and Methods:* Historical twinning rates have been collected from population statistics, made available online by Statistics Norway, while rates from 1967 onwards are from the Medical Birth Registry of Norway. We will adjust for ART, maternal age, parity and smoking for periods where this information is available, using direct and indirect standardization techniques, and standard methods for analyzing rates. *Results:* Preliminary analyses show that for the whole observation time, the mean twinning rate was 1.25%, but with large fluctuations, including periods with rates comparable to those seen today. For the latest period, the twin rate, adjusted for ART, remains considerably higher than 30 years ago, from about 1% in 1987 to 1.4% in early 2010. *Conclusion:* In order to assess this increase or rate level, one should take into account available historical data. A further understanding of the historical rates will be a guide to interpreting present rates and eventual increases or decreases. We will also assess and discuss the ratio of monozygotic twinning to dizygotic twinning where data supports the use of Weinberg's differential rule.

CONTRIBUTION OF GENETICS AND OF ENVIRONMENTAL EXPOSURES TO THE ACTIVITY OF THE DNA REPAIR ENZYME OGG1 IN TWINS

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Introduction: Cells are exposed to the action of endogenous or exogenous agents that, especially through high reactive radicals, cause DNA damage. To counteract these insults, cells rely on an antioxidant defense system and on several DNA repair pathways that ensure genome stability and avoid accumulation of mutations. Great variation of DNA repair capacity (DRC) can be observed in the human population. Reduced DRC is a risk factor for a number of diseases, including cancer. Thus, functional assays for specific repair enzymes have recently emerged as epidemiology-grade, robust and reproducible method to identify population at risk. Here we focused on the functional activity of the 8-oxoguanine DNA glycosylase (OGG1) that removes 8-oxoguanine, the main oxidative damage from DNA. We aimed to estimate the contribution of genetics and environmental exposures on OGG1 activity variance. We also assessed the effect of specific factors that either inhibit OGG1 activity or may modify levels of oxidative stress. *Materials and Methods:* OGG1 activity was measured on lymphocyte protein extracts of 106 Italian twins (37 monozygotic (MZ), 16 dizygotic (DZ) pairs) according to Paz Elizur (2006). The contributions of genetic and environmental effects were assessed using standard univariate twin modeling based on linear structural equations. *Results:* Enzymatic activity of OGG1 significantly decreased with age, while it was not affected by gender, zygosity, smoking habits and body mass index. OGG1 activity was highly correlated both in MZ (r = .77) and in DZ (r = .66) pairs, suggesting that shared (C) and unshared (E) environmental factors substantially contributed to total variance (best model: C = 72%; 95%CI: 57–83, E = 28%; 95%CI: 17–43). When age at enrolment was incorporated in the model as a variance component, it accounted for 6% of the total variance and a slight reduction of C was observed. Birth weight correlated with OGG1 activity (N = 97; coefficient = -0.0002; $p < .001$) and, when introduced as a covariate in the model, markedly reduced C estimate (36%; 95%CI: 0–79). We also found that OGG1 activity was inversely correlated with blood levels of manganese (Coefficient = -0.03; p = .008) and cadmium (Coefficient = -0.16; p = .009). Instead, blood ferritin level and neutrophil granulocyte number, both markers of inflammation, did not associate with enzyme activity. *Conclusion:* Our data show a substantial role of shared environmental factors in the total OGG1 activity variance that is not explained by twins' age. Interestingly, birth weight was inversely correlated with OGG1 activity. Alterations in the antioxidant defense system have been reported as a signature of premature birth (Alexandre-Gouabau, 2013; Minghetti, 2013). Our study suggests that the activity of OGG1 is part of this signature with possible impact on health in adulthood. Moreover, exogenous environmental factors such as cadmium and manganese are associated with decreased OGG1 activity. Cd(2 +) cations have been shown to dramatically affect the catalytic rate constant of OGG1 in vitro (Zharkov & Rosenquist, 2002) and OGG1 function is essential for cell protection by manganese toxicity (Cardozo-Pelaez, 2005). In conclusion, we provide evidence that in humans the activity of OGG1 is mostly determined by endogenous and exogenous environmental factors.

CROSS-CULTURAL GENETIC-INFORMATIVE STUDY OF PERSONALITY TRAITS

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Introduction: The results of the 'Big Five' personality traits studies are often reproduced by different authors, regardless of culture, age, gender. Despite this fact, there are contradictory data on such researches (Riemann et al., 1997, Jang et al., 1998, Borkenau et al., 2001, Vernon et al., 2008, Horsburgh et al., 2009, Distel et al., 2009, Rushton et al., 2009, Kandler et al., 2009, Moore et al., 2010). *Materials and Methods:* We aimed our study at assessing the nature and nurture of personality traits in new (in this sense) populations. For this purpose, we used the NEO-PI-R questionnaire (R.R. McCrae, P.T. Costa, Jr.) in Russian-language adaptation (Oryol & Senin, 2008). There were two samples: the first one included 300 twins from Russia (58 pairs of monozygotic twins and 92 dizygotic twin pairs); the second sample included 222 twins from Kyrgyzstan (45 pairs of monozygotic twins and 66 dizygotic twin pairs), aged from 14 to 29 years old. *Results:* The cultures of these two countries are historically very different: Kyrgyzstan is a nomadic system with strong tribal traditions in which women hold a special position. The Extraversion and Openness factors have shown statistically

significant cross-cultural differences (in ANOVA, Levene's test) while the indicators of the other three factors (Neuroticism, Agreeableness and Consciousness) have not varied as much. The explanation of such differences lies in the considerable distinctions between Russian and Kyrgyz female subsamples. At the same time, no significant differences were found between the male subsamples. Model-fitting was used to estimate the contributions of genetic and environmental influences. The individual differences in the Russian sample in the Agreeableness factor were explained by additive genetic (49%) and non-shared environmental (51%) effects. Other scales contributed additive genetic (18–49%), shared environmental (until 20%) and nonshared environmental (50–62%) effects. The results of the Kyrgyz sample were different. For the Neuroticism factor, 57% was explained by additive genetic and 43% by nonshared environmental effects only; while all three groups of effects contributed to other scales: additive genetic (21–51%), shared environmental (until 35%) and nonshared environmental (43–53%). *Conclusion:* We also found the cross-cultural differences between men and women in the nature of the Big Five personality traits. For example, the Neuroticism factor on the subsample of Russian women was explained by environmental effects only, while both additive genetic and nonshared environmental effects contributed to this factor in the subsample of Kyrgyz women. There were no such differences between Russian and Kyrgyz men. Our results, obtained from Russian and Kyrgyz samples, differ from some results of authors in other cultures. The results of our study suggest that the genetic and environmental influences on the individual differences of the Big Five personality traits vary in diverse populations and also between men and women.

SIBLING RELATIONSHIPS AT 3 YEARS OLD AFFECT THEORY OF MIND AT 4 YEARS OLD AMONG JAPANESE TWINS

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Introduction: Previous studies that siblings of different ages participated in have clarified that sibling relationships are important for the development of theory of mind (ToM; e.g., Cutting & Dunn, 1999). Peterson (2000) pointed that different roles between older sibling and younger sibling are important for ToM. Deneault et al. (2008) said that twin sibling interactions lack variety in anticipating intentions and perspectives. However, how twin sibling relationships affect ToM has not been understood. *Materials and Methods:* 64 MZ pairs and 57 DZ pairs participated at two time points (Time 1: Mean age = 3.06, $SD = .05$; Time 2: $M = 4.09$, $SD = .07$). Sibling relationships were measured at 3 years old by behavioral observation of sibling play at home. ToM was measured at 4 years by three false-belief tasks. We conducted an exploratory factor analysis to clarify the structure of sibling relationships. Then, we compared the effect of twin sibling relationships at 3 years on ToM at 4 years between MZs and DZs by simultaneous path analysis. *Results:* As a result of factor analysis, sibling relationships consisted of three factors: 'clearly sharing goals and intentions', 'positive and equal interaction', and 'sibling negativity'. As a result of simultaneous path analysis, both in MZs and DZs, positive and equal interaction at 3 years promoted the development of ToM at 4 years, and that clearly sharing goals and intentions and sibling negativity at 3 years did not affect ToM at 4 years. There were no differences between MZs and DZs. *Conclusion:* This study indicated that twin sibling relationships at 3 years affected ToM at 4 years. In particular, we showed that having many positive sibling interactions were important for the following development of ToM. In addition, negative interactions between twins did not affect ToM, which was different from the previous studies that siblings of different ages participated. Negative interactions between twins may play a different role from those between siblings of different ages.

ASSOCIATIONS BETWEEN SHORT-TERM MEMORY AND FOOD GROUP INTAKES INDEPENDENT OF GENETIC AND FAMILY ENVIRONMENTAL FACTORS

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Introduction: Previous studies have showed associations between some food group intakes and cognitive function. However, previous studies have not considered effects of genetic and family environmental factors on the associations. In addition, low short-term memory is a clinical feature of dementia and useful for screening for mild cognitive impairment and dementia. Therefore, this study aimed to investigate associations between short-term memory and food group intakes that were not confounded by genetic and family environmental factors. *Materials and Methods:* 172 monozygotic twin pairs aged 20 years old or over were recruited at the Osaka University Center for Twin Research. We measured short-term memory as an outcome and food group intakes estimated per day as predictors. Regression analyses were performed, adjusted for genetic and family environmental factors, and used monozygotic twin differences scores of the outcome and predictors. *Results:* In females, there were no significant associations between short-term memory and food group intakes. In males, short-term memory was significantly associated with intakes of cereals, dairy products, fruits, and pulses. The standardized regression coefficients were as follows: -0.37 (95% CI, -0.64,-0.11) for cereals, 0.29 (95%CI, 0.05,0.58) for pulses, 0.27 (95% CI, 0.01,0.55) for fruits, and 0.31 (95%CI, 0.01,0.56) for dairy products. *Conclusion:* Decreasing intake of cereals and increasing intake of dairy products, fruits, and pulses may be useful for preventing cognitive decline, independent of genetic and family environmental factors in males.

GENETIC AND ENVIRONMENTAL INFLUENCES ON THE SUBJECTIVE WELL-BEING INVENTORY IN JAPANESE ADULTS

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Introduction: The Subjective Well-Being Inventory (SUBI) measures well-being and ill-being (Nagpal & Sell, 1992). Previous studies have reported that negative affect, such as depression, and positive affect, such as life satisfaction, are not necessarily connected (Bradburn, 1969; Jorn et al., 1990). To better understand the relationship between well-being and ill-being, we aimed to study the shared genetic and environmental influences between positive and negative affect of SUBI by using classical twin modeling. *Materials and Methods:* Our study cohort included 216 Japanese twin pairs 20 years or older (195 MZ pairs and 21 DZ pairs). We conducted the SUBI questionnaire consisting two domains (11 factorial dimension, 40 items, 3-level Likert scale). Bivariate Cholesky decomposition was used to analyze genetic and environmental contributions to the positive and negative affect of SUBI and their covariation. Statistical modeling were carried out by R, version 2.15.0, and OpenMx. *Results:* The mean age of the population was 53.9 ± 18.5 years, and 71% of the participants were females. In Bivariate Cholesky Modeling, the fit of both ACE and AE models were good as compared to the saturated model. The results suggested that subjective well-being

and ill-being have significant shared additive genetic and specific environmental components. Independent additive genetic and specific environmental factors also influenced ill-being. Well-being has only a significant association with specific environmental factors. The effects of specific environmental factors were larger than the effects of additive genetic factors. *Conclusion:* The findings show that well-being and ill-being measured by the SUBI share some common additive genetic and specific environmental factors. Further study is needed to find which specific environmental factors influence both well-being and ill-being.

FATAL CHILD MALTREATMENT ASSOCIATED WITH MULTIPLE BIRTHS IN JAPAN: NATIONWIDE DATA BETWEEN JULY 2003 AND MARCH 2012

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Introduction: The purpose of the present study was to clarify the impact of multiple births in fatal child maltreatment, and also to clarify the characteristics of fatal child maltreatment in families with multiple births. *Materials and Methods:* The national annual reports on fatal child maltreatment, which contain all cases from July 2003 to March 2012, published by the Ministry of Health, Labor and Welfare of Japan, were used as the initial sources of information. Multiple births were regarded as the exposed groups. The relative risks (RRs) and their 95% confidence intervals (CIs) were estimated using the data from the above reports and vital statistics. Moreover, an exhaustive information search using newspaper was performed to find multiple births cases and to create a full profile for each multiple-birth case. *Results:* Among 437 fatal child maltreatment cases, 14 multiple births from 13 families were identified. The RRs of multiple births were 2.2 (95% CI 1.2–398) per individual and 4.0 (95% CI 2.2–7.4) per family. The 14 multiple-birth victims were all twins. No significant difference between twins and singletons with fatal maltreatment was observed for most characteristics. However, in the case of twins, 0-month victims were significantly rarer, and the number of children per family was significantly larger. The victim's siblings were also maltreated in 6 out of the 12 relevant cases, including all 6 co-twins. Premature birth, having a disabled co-twin, delay of growth or development and parental disfavor tended to be factors of maltreatment when only one twin was maltreated. *Conclusion:* Families with multiple births had elevated risk for fatal child maltreatment. The non-specific overburden of child rearing might be one possible reason for the higher frequency of child maltreatment for multiples compared to singletons; comparisons between the two twins might be another.

LIFE SATISFACTION AND WORK ABSENTEEISM – A DISCORDANT TWIN ANALYSIS

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Introduction: For the past years, data from population-based twin registries have become increasingly important in studies of work absence, which is a major public health and economic challenge in many developed countries. Sick leave (SL) and disability pension (DP) are influenced by a wide range of medical, psychological and psychosocial factors, but little is known about how life satisfaction affects absenteeism. This study employs a discordant twin design to explore to what degree life satisfaction predicts DP and SL in young adults, independently of symptoms of common mental and somatic disorders. *Materials and Methods:* In the Norwegian twin registry, data from questionnaires and interviews from 7,698 young adults have been linked to highly reliable official registries on long-term sick leave (LTSL) and disability pensioning (DP) between 1998 and 2008. Data on life satisfaction (a 6-point scale from *very unsatisfied* to *very satisfied*), mental distress (SCL-5), and musculoskeletal pain (lumbar spine, neck/shoulder and muscular pain) were retrieved from a 1998 questionnaire, thus obtaining a prospective design. For SL we constructed a variable reflecting the proportion of days employed (eligible for sick leave) the subject was on LTSL. For the preliminary analyses, we used logistic regression models with DP and having high levels of LTSL (more than 10%) as dependent variables, first corrected for dependency by GEE and subsequently using the 'fixed effects' option in STATA for the discordant twin design. *Results:* After excluding subjects who got their DP prior to year 2000 ($n = 72$) the final sample included 7,626 twins, including 3,055 complete pairs and 1,516 singletons. Forty-two percent were male, and mean age at last follow-up (2008) was 35.5 years (range 29–41). By 2008, 181 subjects had received DP, and 63.7% of the sample (47.4% of males and 76.0% of females) had at least one period of LTSL. Preliminary results showed that adjusted for age, sex and educational attainment, life satisfaction was significantly negatively associated with both DP and LTSL (OR for each level of increasing LS 0.59, CI 0.51–0.65 and 0.78, CI 0.73–0.82 respectively). The associations remained significant after adjusting for mental distress and musculoskeletal complaints (ORs 0.72, CI 0.61–0.85, and 0.91, CI 0.85–0.98). In the discordant twin analyses, the associations remained significant with similar effect sizes when all zygosity groups were analyzed together (ORs 0.68, CI 0.47–0.98 and 0.85 CI 0.74–0.97). Further analyses will be presented at the conference. *Conclusion:* Life satisfaction seems to protect against work absenteeism in young adults, independently of symptoms of common mental and somatic disorders, and independently of common environmental and possibly genetic confounding.

MONOCHORIONIC PLACENTAS: ARE THEY ALL THE SAME?

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Introduction: Monochorionic twins share a single pacenta with intertwin vascular anastomoses. These anastomoses may allow blood transfusions from one fetus to another and vice-versa and result in complications such as twin-twin transfusion syndrome (TTTS). There are several forms of TTTS; the most well known is the twin oligopolyhydramnios sequence (TOPS). In 2007, a new form of chronic TTTS, termed twin anemia-polycythemia sequence (TAPS), was described. Unlike TTTS, TAPS placentas appear to have a unique angioarquitecture, so that the postnatal diagnosis of TAPS is based on the presence of (chronic) anemia in the donor and polycythemia in the recipient, in association with typical placental angioarchitecture as identified by injection with colored dye. *Materials and Methods:* In our study, we analyzed the placental angioarchitecture of a randomized sample of monochorionic placentas (MC placentas), examined at our center between January 2013 and March 2014. Placental angioarchitecture was analyzed using colored dye injection. *Results:* A total of 12 MC placentas were injected, of which 2 fulfilled the diagnosis criteria for posnatal TAPS and the other 10 corresponded to uncomplicated MC twin pregnancies (without TTTS). Both TAPS cases occurred spontaneously. The number of anastomoses per placenta was 3.5 (3–4) in TAPS placentas and 4 (2–6) in the rest (value given as median [range]). TAPS placentas had a total of 7 anastomoses, all arteriovenous (AV) anastomoses and 6 with a diameter $\leq$1 mm. The rest of placentas had a total of 35 anastomoses: 10 AA, 1 veno-venous and 24 AV. In this group only 14 anastomoses had a diameter $\leq$1 mm. *Conclusion:* The small sample is an important limitation of

our study, however, we would like to emphasize the absence of AA anastomoses and the higher incidence of anastomoses with diameter of ≤1 mm in TAPS placentas (85% vs. 40%). Our study may also suggest that the incidence of spontaneous TAPS could be higher than the 3–5% pointed to in the literature.

SELF-REPORTED DIETARY INTAKE PATTERNS CORRELATE STRONGLY WITH BLOOD METABOLITES USING A NON-TARGETED METABOLOMICS APPROACH IN A POPULATION-BASED TWIN STUDY

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Introduction: Prompted by the inaccuracies of self-reported dietary intakes, metabolomics has become a primary tool for food intake biomarker discovery. Within nutritional epidemiology, interest in dietary patterns has increased, particularly for their ability to measure the whole diet and the subsequent impact on health. Using a targeted metabolomics approach (163 metabolites), we have previously identified significant dietary pattern-metabolite associations. In this study, we assess, using a non-targeted metabolomic platform, the extent to which metabolomic profiles are correlated with nutritional patterns generated through principle component analysis (PCA) and with the Mediterranean diet score (MDS), a strong predictor of health outcomes. *Materials and Methods:* The validated EPIC-Norfolk 131-item Food frequency questionnaires (FFQ) was applied to 2,517 females from TwinsUK with fasting plasma metabolomics profiling available using the Metabolon platform (281 known metabolites). Previous PCA of the FFQs generated five top PCs (accounting for 22% of the variance): fruit and vegetable; high alcohol; 'traditional English' (high intakes of fried fish and potatoes, meats, savoury pies and cruciferous vegetables); dieting; and low meat. The MDS was calculated using the method outlined by Trichopoulou et al. Through linear regression analysis, the correlation between each metabolite and the 6 dietary patterns was assessed in the larger population (discovery), excluding monozygotic (MZ) twins discordant (1 *SD*) for each dietary pattern (n = 107 to 222 pairs). Significant diet-metabolite correlations (Bonferroni: 0.05/[6 dietary patterns x 281 metabolites] = 3.0×10^-5) from the first analysis were then replicated in the MZ discordant pairs. Results of both analyses were then meta-analysed. *Results:* 82 metabolite-diet pattern associations were confirmed: 26 for fruit and vegetable; 19 for high alcohol; 16 for MDS; 12 for low meat; 7 for traditional English; and 2 for dieting. The strongest associations were found between a high alcohol diet and alpha-hydroxyisovalerate (Beta = 0.165, SE = 0.01, p = 1.16×10^-35), an amino acid involved in the valine, leucine and isoleucine metabolism, and between the fruit and vegetable diet pattern and glycerate (Beta = 0.100, SE = 0.01, p = 4.60 × 10^-26), a key carbohydrate intermediate in the glycolysis pathway. Numerous metabolites were associated with multiple diet patterns, such as: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), 1-docosahexaenylglycerophosphatidylcholine, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF), indolepropionate, glycerate, pyridoxine, 1,5-anhydroglucitol, hippurate, threonate and scyllo-inositol, suggesting these metabolites are highly sensitive to dietary intakes. Among these, DHA, EPA, 1-docosahexaenylglycerophosphatidylcholine and CMPF have previously been strongly associated with fish intake and are involved in essential fatty acid metabolism. *Conclusion:* Our data indicate that there is a strong relationship between metabolites and dietary patterns generated through data-driven and a priori analyses of FFQs, thus suggesting that metabolomic studies can be used to assess the role of nutrients and to include this component in OMICs research. Combined with clinical data the metabolomic approach may generate biomarkers of early disease, or nutritional status. In addition, our results support the utility of non-targeted metabolomic approaches for use in nutritional epidemiological studies. Our study consists of women only, so results may not be applicable to men.

WHERE WERE TWINS BORN IN HUNGARY? REGIONAL ASPECTS SINCE 1970

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Introduction: The national statistical data on twin and multiple (TAM) births and deliveries have been registered since 1876 in Hungary. Although there were some years during this 138-year period when vital statistics for twin births and deliveries were left out, the trends can be followed, except for the period of World War II. The past 4 decades trends of twinning are summarized, relying on official statistical data since 1970. Notably, the TAM birth rate rose following the Act CLIV of 1997 on Health. The Act provided state support for assisted reproduction treatments, which spectacularly increased the ratio of twins — and especially of triplets — among live births. The trend has been turned since 2009–2010 and a decreasing era of TAM births seems to have started. Twinning rates are higher in the western counties, the capital and its suburbs, and lower in the eastern counties. *Materials and Methods:* The study was based on the Hungarian Central Statistical Office's data. The method was based on comparing and counting twinning rates in regions and counties. *Results:* The twinning rate started to increase in the mid-1990s as a result of changes in childbearing habits. There was no significant difference in twinning rates between settlement types (e.g., smaller towns and villages, towns of county rank, capital city) before the mentioned period. The twinning rate varied between 18% and 25%. After the mid-1990s, however, the twinning rate was above the national average in the capital city and in towns with county rank, while in smaller towns and villages, although the twinning rate also increased, it was below the average. The twinning rate in Budapest is higher than the national average, but there are large differences among the capital's districts. In 1990, the northeast districts of the city and the 1st and the 18th districts had above-average twinning rates. Except for the central districts, where the figures were below the national average, most districts in Budapest had above-average rates in 2012. *Conclusion:* There is a geographic correlation between regional prosperity and high twinning rates in Hungary in the past decade. Cities and counties with GDP and personal income higher than the national average — generally the capital and other principal cities, as well as the counties in the northwestern part of the country — have higher twinning rate. Regional differences in prosperity have increased dramatically since 1990, after the regime change, and they had an effect such social phenomena as childbearing patterns. In the few decades before 1990 (the Kádár era), regional (and other) differences in financial resources available to families were not pronounced. There were, correspondingly, no significant regional disparities among twinning rates either. But, after some years following the regime change, the twinning rate became higher in those areas where personal incomes were higher. Naturally, mothers' age at childbearing changed, too, in the past decades.

THE ASSOCIATION BETWEEN MID-TRIMESTER CERVICAL LENGTH, MATERNAL SYSTEMIC AND PLACENTAL INFLAMMATION, AND PRETERM BIRTH IN TWIN PREGNANCIES

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Introduction: In twin pregnancies, a short mid-trimester cervical length is one of the most important risk factors for spontaneous preterm birth (SPTB). Maternal systemic inflammation as measured by C-reactive protein (CRP) and placental inflammation are associated with SPTB in women presenting either with symptoms of labor or ruptured membranes. However, the relationship between mid-trimester cervical length, maternal systemic and placental inflammation, and SPTB is not known. The purpose of this study was to determine whether a short mid-trimester cervical length ($\leq$ 2.5cm) is associated with SPTB (defined as a gestational age at delivery $\leq$32 weeks) independent of subsequent maternal systemic and placental inflammation in twin pregnancies complicated by preterm labor or preterm premature rupture of membranes (PPROM). *Materials and Methods:* This is a retrospective cohort study of 76 consecutive women with twin gestations who underwent routine cervical length assessment between 20 and 25 weeks of gestation and who were thereafter admitted with preterm labor or PPROM. CRP levels were determined on admission and the placentas were examined histologically after delivery. Bivariable and multivariable analyses were used to investigate independent associations with SPTB. *Results:* Of the 76 women who met inclusion criteria, 21 (27%) had SPTB at $\leq$32 weeks and 14 (18%) had a short cervix at mid-trimester. Women with a SPTB at $\leq$32 weeks' gestation had significantly higher incidence of short cervix and histologic chorioamnionitis, a higher mean serum CRP level, and a lower mean gestational age at the time of admission than those who did not deliver spontaneously at <32 weeks' gestation. In multivariable regression, a short cervix was significantly associated with SPTB after controlling for histologic chorioamnionitis, elevated level of serum CRP on the clinical presentation, and lower gestational age on admission. *Conclusion:* In twin gestations complicated by preterm labor or PPROM, a short cervix detected at mid-trimester ultrasound was associated with SPTB independent of subsequent maternal systemic and placental inflammation. These data suggest that the risk of SPTB associated with a short mid-trimester cervix is due to different mechanisms, rather than infection/inflammation.

CRITICAL STEPS OF LASER THERAPY FOR TWIN-TO-TWIN TRANSFUSION SYNDROME: A DELPHI SURVEY

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Introduction: Fetoscopic laser surgery for twin-to-twin transfusion syndrome (TTTS) is an invasive, highly specialized procedure for which no objective tools exist to assess technical skills. The aim of this study was: (1) to determine expert consensus regarding items required for an evidence-based training curriculum for fetal surgeons; (2) to create an instrument that can be used to evaluate technical performance in laser surgery. *Materials and Methods:* A Delphi survey was conducted among an international panel of experts ($n = 98$) in fetoscopic laser surgery. Experts rated the substeps of laser therapy on a 5-point Likert-type scale and were able to comment on each substep. Responses were returned to the panel until consensus was reached (Crohnbach's $\alpha \geq .80$). All substeps that 80% of experts rated as $\geq$4 were included in the evaluation instrument. *Results:* Two survey rounds were completed with 73/98 (74%) experts worldwide (round 1) and 66/73 (90%; round 2). Overall consensus was high for both rounds ($\alpha \geq .80$) Respondents mean (range) experience with laser was 10.2 years (5–25). After round 1, consensus had been reached on 50 of the 81 items. In the second iteration, some questions were merged and 23 items had to be rerated. A total of 55 defined steps in 18 domains were included in the final consensus list. A final round obtained the order of importance of the substeps. *Conclusion:* Laser surgery is currently accepted as the best, most effective and safest possible treatment modality for TTTS. Consensus on a uniform framework for a standardized approach to teach laser surgery was achieved within a representative group of fetal surgeons. This instrument can be used to evaluate a surgeon's technical performance in fetoscopic laser therapy, both in a high-fidelity simulator training model as in real-life situations.

DEPRESSION SYMPTOMATOLOGY AND COGNITIVE DECLINE: A 10-YEAR FOLLOW-UP STUDY OF DANISH TWINS TO IDENTIFY SHARED ETIOLOGY

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Introduction: Staying in good mental health is essential for the maintenance of a good life quality from middle-age through to the oldest ages. Previous research demonstrates a large degree of cross-sectional correlation between depression symptoms and cognitive function, and it has been suggested that depression can serve as a risk factor for dementia and Alzheimer's disease. However, it is still not clear whether depressed mood directly increases the risk of dementia or depression is a prodromal sign of an evolving cognitive impairment, or whether the two conditions share common pathological mechanisms or pathways. Here we have used 10-year follow-up data from middle-aged Danish twins to elucidate whether decline in cognitive function and increase in depressive symptoms share common underlying genetic mechanisms that affect the baseline level as well as the rate of change of the phenotypes. *Materials and Methods:* The study included 2,866 twins with a mean age of 56.8 years at intake. Of these 1,267 were intact pairs. A total of 1,582 twins (55%), of which 557 were intact pairs, participated in the follow-up after 10 years. The cognitive composite score was based on performance in six subtests — forward and backward digit recall, immediate and delayed recall of 12 nouns, number of animals mentioned in 1 minute, and symbol-digit replacement. The affective depression score was based on 9 questions about happiness, loneliness, future expectations, worriedness, and feeling of worthlessness, tenseness, and nervousness. Heritability estimates as well as the genetic correlations were estimated using a growth curve model based on structural equation models of age- and sex- adjusted residuals using the Mx software. *Results:* The best fitting model for the heritability analysis was an AE model. The heritability of the intake level of cognitive function and affective depression symptoms was 0.62 (95%CI: 0.57–0.66) and 0.28 (95%CI: 0.21–0.34), respectively. The heritability of cognitive decline was 0.14 (95%CI: 0.05–0.23), whereas there was no significant genetic contribution to the 10-year change of depression score. There was a small, but statistically significant, genetic correlation between level of

cognition and affective depression state (rg = -0.15, 95%CI: -0.27–0.03), which accounted for approximately 58% of the phenotypic correlation between the two phenotypes. Contrary to this, the correlation between cognitive decline and changes in depression symptoms over 10 years was mainly due to a unique environment influencing both phenotypes. *Conclusion:* The level of cognitive function and affective depressive symptoms is more heritable than the rate of change. In addition, there is a moderate correlation between the level of cognitive function and affective depressive symptoms, and a substantial part of this correlation can be attributed to shared genetics.

INTRAUTERINE FETAL DEATH IN TWINS: CHORIONICITY DEPENDENT OR NOT?

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Introduction: During the last decade, the percentage of twin pregnancies has increased and reached 3% of all pregnancies presented. The goal: Our study was to analyze twin pregnancies in which there was a intrauterine fetal demise of one twin, show the course and outcome of pregnancy, as well as possible reasons for loss of a fetus *Materials and Methods:* This study enrolled 36 twin pregnancies that were delivered at the Obstetrics and Gynecology Clinical Center in a 5-year period. Pregnant women were divided in two groups of patients similar by age, parity, and as a way of creation and termination of the pregnancy. The first group included 15 patients with monochorionic twin pregnancy, and the second group consisted of 21 patients with dichprionic twin pregnancies. *Results:* The mother's age increased the chance of developing a twin pregnancy. A previous pregnancy with the same outcome represented a risk factor for fetal loss again. Majority monochorionic twins came from natural conception (2 IVF vs. 13 natural). Dychorionic twins are more often result of IVF (9 IVF vs. 12 natural). The average duration of fetal death was 4.8 weeks in the first group and 6.3 weeks in the second. Doppler measurements showed increased resistance index in umbilical artery and decreased RI in MCA in 66% of cases.Three-quarters of pregnancies ended in term by cesarean section. *Conclusion:* The most common reason for the loss of one twin according to our autopsy report is a chronic placental failure, but in MC twins, it is TTTS and prematurity.

CARDIOVASCULAR STATUS IN MULTIPLE PREGNANCIES COMPLICATED WITH TWIN-TWIN TRANSFUSION SYNDROME

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Introduction: Twin-twin transfusion syndrome (TTTS) complicates 10–17% of monochorionic diamniotic twin (MCDA) pregnancies. The major issue in this condition is the increase of preload in recipient twin and the decrease of preload in the donor. As a result functional and structural changes in both twins are observed. Aim of the study: To check for cardiovascular signs in multiple pregnancies complicated with TTTS. *Materials and Methods:* We examined latest cases of TTTS admitted to our institution before qualification for further management. Our study population included 36 cases of MCDA twins and one case of dichorionictriamniotic triplets between 16 and 23 weeks of gestation. All subjects were staged according to Quintero classification. We utilized GE Voluson E6 ultrasound system equipped with hybrid 4–8 MHz transducer. Our study protocol in the donor twin covered: umbilical artery (UA), middle cerebral artery (MCA) and umbilical vein (UV) Doppler velocimetry; in the recipient twin: ductusvenosus (DV), UV, tricuspid, mitral, main pulmonary artery Doppler velocimetry. In all co-twins, structure of the fetal heart was evaluated. *Results:* Distribution of TTTS stages observed in our population was: 19 patients with stage I, 11 with stage II, 4 in stage III, 2 in stage IV, and 1 in stage V. The most common peripheral Doppler findings in donor twins were absent end diastolic flow (AEDF) in UA (5 patients out of 6 from stage III and IV). Donor twins did not reveal any central cardiovascular abnormalities. In recipients among the most frequent peripheral Doppler findings negative and reverse a-wave in DV was observed (all cases in stage III and IV). Regarding cardiac functional abnormalities tricuspid regurgitation (9 cases in stage II, in all subjects in stages III and IV); and monophasic tricuspid flow (1 in stage I, 6 cases in stage II, and in 4 in stages III and IV) were the commonest. Concerning cardiac structure, ventricular hypertrophy was found in 21 cases (2 in stage I, 13 in stage II, 6 in cases III and IV). *Conclusion:* Total functional cardiovascular abnormalities are more common findings than peripheral Doppler dysfunctions. We suggest implementing central functional observations into routine assessment of TTTS.

A COMMON DNA METHYLATION SIGNATURE IN WHOLE BLOOD SAMPLES FROM MONOZYGOTIC TWINS DISCORDANT FOR MALIGNANT TUMOUR DEVELOPMENT

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Introduction: It is now generally accepted that tumor development involves both genetic and epigenetic changes. Cancer cells show aberrant global and specific epigenetic changes and are pivotal events in many types of cancers. Several studies have identified DNA methylation changes in non-invasive tissues, such as blood or sputum, for specific cancer types. However a pan-cancer DNA methylation marker, common to multiple types of cancer, has not yet been identified. The aim of this study was to identify pan-cancer specific differentially methylated positions (cDMPs) in whole blood samples using 38 MZ twin-pairs discordant for cancers of multiple origins. *Materials and Methods:* We performed an epigenome-wide study using the HumanMethylation450 BeadChip to determine cDMPs in whole blood for 38 MZ twin pairs discordant for invasive cancers of 8 different origins (breast, colorectal, ovary, cervix, skin, uterus, thyroid, and pancreas). After quality control checks, we adjusted for cell heterogeneity using principle component analysis and fitted a linear regression model using the first 8 principle components (PCs). These PCs were correlated with estimated and empirical cell count data as well as batch effects, but not to cancer status. The methylation residuals were calculated from this model and a one-sample *t* test was applied on the difference per twin pair. *Results:* Six suggestive cDMPs ($p < 1e-5$) were identified that fall within four genes (cg27094856 in AXL, $p = 5.0e-6$; cg08897368, $p = 5.48e-6$; cg04111177 in NR3C1, $p = 5.62e-6$; cg19677259 in MTL5, $p = 6.47e-6$; cg15696973, $p = 7.49e-6$; cg26741280 in SLC6A4, $p = 7.88e-6$). Interestingly, the top ranked result (cg27094856) showed higher DNA methylation levels in the cancer-affected twin and was located in an intragenic region of the gene AXL receptor tyrosine kinase (AXL) that is a well-known oncogene and implicated in increased malignancy of many cancers. Data from ENCODE showed the cDMP is located within a poised promoter in a CpG Island shore, indicating DNA methylation involvement in either splicing events or this alternative promoter, including up to seven exons following the cDMP. We performed a case control study in independent, unrelated individuals and observed a similar trend of higher DNA methylation in cancer-associated individuals. *Conclusion:* In conclusion, we aimed to identify an epigenetic signature common to

cancers of multiple origins in whole blood using cancer discordant MZ twin-pairs. Using Bonferroni correction ($p < 1e-7$) or FDR threshold of 5%, no epigenome-wide significant associations were identified, however, our peak results revealed 6 suggestive cDMPs. The top-ranked result is located in a well-established oncogene in cancer tissues, AXL.

GENES, PERSONALITY AND LIFE SATISFACTION

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Introduction: Life satisfaction (LS) is influenced by personality traits. The Big Five traits of Neuroticism and Extraversion appear particularly important. However, the nature of these associations is not fully known. The aim of our study was to (1) identify the most important personality facets driving the effects, and (2) to examine the role of genetic and environmental factors in these associations. *Materials and Methods:* Questionnaire data were collected among 1,516 twins (aged 50–65, response rate 71%) drawn from the Norwegian Twin Registry. Personality traits and facets were measured by the NEO-PI-R. LS was measured with the Satisfaction With Life Scale. Regression analyses were applied to identify personality facets uniquely predicting LS, and Cholesky models were used to estimate genetic and environmental influences. *Results:* The effect of personality on LS was mainly driven by four specific facets: the Neuroticism facets of Anxiety and Depression, and the Extraversion facets of Positive Emotions and Activity. These facets explained 33% of the variance in LS. Heritability of LS was .31 (CI: .22–.40), and genetic factors accounted for 61% of the covariance between personality and LS. Also, LS was found to have a unique genetic component, unrelated to personality. *Conclusion:* LS is influenced by genetic factors, but possibly to a lesser degree than other components of subjective wellbeing. Personality factors and facets account for a substantial amount of variance in LS. These associations are mainly due to emotional aspects of personality, and the associations are strongly influenced by genetic factors. However, the genetic effects on LS are not fully accounted for by personality related genes.

THE INFLUENCE OF GENOMIC VARIABILITY ON PHENOTYPIC DISCORDANCE — TOWARDS POLISH REGISTRY OF MONOZYGOTIC TWINS (MZT) DISCORDANT FOR CHRONIC MEDICALLY RELEVANT CONDITIONS

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Introduction/Background: Monozygotic twins discordant for a phenotype/disease provide a unique opportunity to dissect genetic/epigenetic factors contributing to human morbidity. The aim of the study is to identify genetic and/or epigenetic variability causing phenotypic differences in MZTs. *Patients and Methods:* The project will implement genome-scale approaches based on state-of-the art next-generation sequencing technology such as whole-genome sequencing, whole exome sequencing, and genome-wide methylation analysis. As the first step, we have started a search for MZT pairs discordant for chronic diseases through a media campaign in Poland. *Results:* So far, 30 MZT pairs interested in participating have been identified. In all but one, zygosity was positively confirmed through analysis of a panel of 16 STR markers. The recurrent medical conditions present in identified twins included inborn defects ($n = 5$), autism ($n = 3$), allergy ($n = 2$), cancer ($n = 3$), SLE ($n = 2$). Among the non-recurrent diseases, the most interesting is a case of biopsy confirmed neuropathy of the Charcot Marie Tooth (CMT) which has been present for ~20 years in a 50-year-old MZT, but not his brother. *Conclusions:* The collection of MZT pairs discordant for medically relevant conditions, including clearly monogenic disorders such as CMT, is feasible. With the assumption that genomes and epigenomes of MZTs are highly similar, linking the identified genetic/epigenetic differences to the disease phenotype should be much less challenging than in any other type of analysis aiming to establish such relationship or lack thereof. Thus, we hope that the planned study will reveal novel (epi)mutations/loci causing human diseases.

UNCONSCIOUS AND EMOTIONAL PROCESSES IN TWIN PREGNANCY

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Introduction: Since the mid-1970s, the number of multiple births has increased in industrialized countries. However, twin pregnancies are associated with a higher incidence of adverse maternal and neonatal outcomes, including increased physical and psychological distress. Pregnancy has an important but often unconscious, emotional impact on women, because of their new physical, psychological and social condition. However, few studies have been carried out on the unconscious dynamics of women expecting a single baby, and even fewer on women expecting twins. The aim of the present study was to use the Lüscher Color Test to examine personality traits and unconscious processes in women with twin and singleton pregnancies attending prenatal classes. *Materials and Methods:* The short version of the Lüscher color test was administered to 100 singleton and 50 twin pregnant Italian women, respectively, following prenatal class in the third trimester. *Results:* Twin and singleton pregnant women chose violet as the most liked color (50 vs. 49%), showing the idealization of the pregnant status; and brown as the most disliked color(52 vs. 44%), expressing physical stress. Conversely, twin pregnant women chose yellow in the second position(28 vs. 17%) and as the most combined, the favorite violet color (44 vs. 19%, p .0006), indicating the wish to give birth soon; singleton pregnant women chose blue as the favorite one(42 vs. 12%, p .00001), indicating the desire to create a bond with their infant. Moreover, they chose red in the third position(34% vs. 17%, p .009), expressing their concern about building a relationship with their babies. In addition, twin and singleton pregnant women preferred form 6, the sine curve on a dark background, but refused the associated brown color 6, revealing the need for attention toward their body against the renunciation of bodily needs satisfaction. Moreover, singleton pregnant women preferred form 3, a dark-contour acute triangle, but refused the associated red color 3, expressing their need to control any aggressive behavior against their baby's unconscious rejection. *Conclusion:* Twin and singleton pregnant women shared the idealization of their pregnant status, although this is perceived as stressful. Conversely, twin pregnant women were afraid of building a relationship with their babies and wanted to give birth soon.

NEUROLOGIC OUTCOME IN A POPULATION OF MONOCHORIONC TWINS

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Introduction: Monochorionic twins are at increased risk of neurologic morbidity related to prematurity and complications of

pregnancy. An increased number of premature infants survive, and the interest in long-term neurodevelopmental outcome is a major issue. Obstetric management of complicated monochorionic pregnancies can require fetal interventions, extensively evaluated in the last few years in term of neonatal morbidity and neurodevelopmental outcome. *Materials and Methods:* We evaluated a population of 174 monochorionic twins born between 2007 and 2012 at V. Buzzi Children's Hospital. All children underwent serial ultrasound scans, pediatric and neuropsychiatric evaluations. MR was performed routinely at 40 weeks of corrected age in all premature babies born under 32 weeks of gestation and in all infants with pathologic ultrasound exams. Neurodevelopmental assessment was performed by the Griffiths scale. In the first 2 years of life we focused on major and minor motor disabilities and severe neurobehavioral impairment. Mild neurobehavioral, cognitive and language disabilities are still under investigation. *Results:* Gestational age ranged from 27.5 to 35.5 weeks (31.1 W). Neonatal weight ranged from 576 g to 2870 g (mean weight 1648 g). Eight infants revealed motor disabilities (5%). Four infants (2.4%) had severe motor impairment (cerebral palsy, GMFCS>2), one infant had moderate (GMFCS = <2) and three had mild disabilities (clumsiness and transient motor delay). The infants with severe motor disabilities had a gestational age over 32 weeks (32,4–35,5W) and the pregnancy was complicated by TTTS (treated with laser surgery in two cases, one with amnioreduction and one received no treatment for acute onset of TTTS). Prenatal brain injuries were recognized in three of the four children described in the severe outcome group (three recipient twins and one donor twin). Two donor and one recipient twin had mild motor disabilities (all born before 28 weeks of gestation). MR abnormalities were found in 28 children (cystic PVL grade 3, mild-moderate PVL, punctate white matter lesions, medullary veins thrombotic lesions, cerebellar injuries). Most children had a Griffiths GQ between 100 and 115 (61.3%), 27.2% had a quotient between 85–99, 9% had a GQ between 116 and 130.Only 2.2 % of children had a GQ below normal range (64–84). Severe neurobehavioral impairment was found in two ELBW infants (autistic disorder), who could not be tested with Griffiths scale. *Conclusion:* In conclusion, most of the children in our study had a normal motor outcome (95%). Severe motor impairment was found in infants born after pregnancy complicated by TTTS. The Griffiths developmental quotient was normal in most twins Mild motor disabilities and neurodevelopmental impairments were more frequently related to premature Birth and ELBW.

THE IMPACT OF GENETIC AND ENVIRONMENTAL FACTORS ON MATERNAL GESTATIONAL WEIGHT GAIN: A TWIN STUDY BASED ON THE SWEDISH TWIN REGISTRY

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Introduction: Gestational weight gain (GWG) is a complex trait, involving intrauterine environmental, maternal environmental and genetic factors — the extent to which these aspects contribute to the total variation in GWG is, however, poorly understood. The primary aim of this study was therefore to examine the genetic and environmental influences on variances in maternal GWG in the first pregnancy of monozygotic (MZ) and dizygotic (DZ) Swedish twin mothers. In order to explore if heritability estimates vary according to pregnancy order we also analyzed the total variation in GWG in the mothers' second pregnancy in a subset of twin mothers. *Materials and Methods:* By using Swedish nation-wide record-linkage data we identified MZ and DZ twin mothers who had given birth to at least one child for the first analysis, and two consecutive children for the second analysis, between the years 1982–1989 and 1992–2010. We used structural equation modelling (SEM), which decomposes the total variation of GWG into additive genetic (A), shared environmental (C) and unique environmental (E) components. *Results:* We used data on 786 complete MZ and 714 complete DZ female twin pairs to estimate heritability in GWG in the first pregnancy and 134 MZ and 117 DZ complete twin pairs with complete data on the second pregnancy. We found that GWG in both the first and second pregnancy showed moderate heritability (0.55 and 0.40 respectively). SEM analyses also revealed that the remaining variation in the trait could be explained merely by unique environmental factors and that the estimate was consequently larger for the second pregnancy compared to the first (E $\approx$ 0.60 and $\approx$ 0.45 respectively). *Conclusion:* This study showed that maternal GWG has a moderate heritability, suggesting that a large part of the variation in the trait can be explained by unique environmental factors such as the mother's diet and lifestyle. From a public health point of view, targeting these factors could therefore provide an opportunity for preventing excess GWG.

USING BIOMARKERS IN POPULATION-BASED STUDIES

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Introduction: New technologies have expanded the possibilities for collection of a range of biospecimens in population-based studies where biological samples are collected in non-clinic settings (e.g., participants' homes). Options to be discussed include collection of: (1) blood samples via fingerpricks for dried blood spots (DBS) and various 'point-of-care' meters, (2) hair samples and (3) various types of performance measures. *Materials and Methods:* Presentation will provide an overview and discussion of technologies and protocols that have been developed for use in field-based population studies in order to assess various major physiological regulatory systems known to be involved in various major pathophysiological processes involved in age-related cardiovascular disease as well as cognitive and physical functioning (e.g., glucose and lipid metabolism as well as inflammation along with neuroendocrine activity). The presentation will also highlight some newly developed technologies that also offer some options for assessments of DNA and RNA related processes, as well as work currently underway to validate use of new microarray technologies to further expand the range of available assays based on blood collection via fingerpricks. *Results:* Salient advantages of these types of biospecimen collection protocols include the fact that they can be done by trained, non-medical research staff and generate health-related information that is frequently of significant interest to participants, such that offering this information results in increased rather than decreased study participation. The advent and validation of these new technologies has resulted in increased collection of biomarker data in multiple large population-based studies. This has also led to development of an international 'Biomarkers in Population Health' research network, which seeks to leverage shared experiences and support for further technology development and validation so as to further enhance opportunities to collect biological information to help in understanding the processes that contribute to international differences and trends in population health. *Conclusion:* New technologies have expanded the possibilities for collection of a range of biospecimens in population-based studies where biological samples are collected in non-clinic settings (e.g., participants' homes). Options include collection of: (1) blood samples via fingerpricks for dried blood spots (DBS) and various 'point-of-care' meters, (2) hair samples and (3) various types of performance measures. Salient advantages of these types of biospecimen collection protocols include the fact that they can be done by trained, non-medical research staff

and generate health-related information that is frequently of significant interest to participants such that offering this information results in increased rather than decreased study participation.

ARE TWINS REARED APART MORE EPIGENETICALLY DISCORDANT THAN TWINS REARED TOGETHER?

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Introduction: Epigenetic change plays a role in development, aging and disease. However, the factors that influence this change are poorly understood. Twin studies have the power to unravel the genetic and environmental components of epigenetic states. They are revealing that epigenetic marks can both be influenced by genetic, shared and nonshared environment. However, evidence for 'epigenetic drift' — age and environment-related epigenetic discordance within pairs of twins — is controversial. We are investigating the phenomenon of epigenetic drift by comparing a unique set of five types of twins: monozygotic (MZ) and dizygotic twins reared apart (MZA and DZA), MZ and DZ twins reared together (MZT and DZT) and 'virtual' twins (VT) — unrelated individuals raised together in the same family very soon after birth. We hypothesize that (1) twins reared apart are more epigenetically discordant than those of a similar age reared together, and that (2) virtual twins are more discordant than DZA co-twins. *Materials and Methods:* We are analyzing the epigenetic marks of DNA methylation in buccal epithelium from a number of MZA, MZT and virtual twins. Bisulfite-converted DNA is being analyzed by locus-specific and genome-wide approaches. Height difference will be used as an approximate phenotypic indicator of intra-pair developmental disruption. *Results:* The current project is a work-in-progress, designed with the goal of attracting additional pairs of these rare twin participants. Age of separation for the reared-apart twins ranged from 1 to 563 days, which can allow us to partly remove the effects of shared postnatal environment on epigenetic and phenotypic similarity. Children (mostly female) were aged 4–14 (Mean = 8.96 + /-3.45 years) when the buccal swabs were collected, providing a unique window into an important period of development up to first menses. Two adult reared-apart twin pairs, one MZA and one DZA, were 25 and 78 years old, respectively, both at reunion and at the time of data collection. Outlining the specific goals and directions at present is key to fulfilling this aim. We also hope to solicit input from colleagues, continuing conversations on twins and epigenetics initiated during the conference pre-session. *Conclusion:* As indicated, it is anticipated that epigenetic differences will be larger between twins raised apart than twins raised together, and greater between twins (regardless of rearing status) than unrelated individuals raised together. We predict that the greatest differences will be found in growth regulatory loci and be manifested phenotypically. Should such findings be confirmed, it will be important to reconcile them with reports of similar levels of resemblance in some physical and behavioral traits (e.g., height and personality) between MZA and MZT twins.

TWIN STUDIES OF TACIT COORDINATION: NEW FINDINGS IN AN ADOLESCENT AND ADULT SAMPLE

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Introduction: Tacit coordination (TC) refers to situations in which 'two parties have identical interests and face the problem not of reconciling interests, but only of coordinating their actions for their mutual benefit when communication is impossible' (Schelling, 1960). Based on principles from kin selection theory, successful coordination should occur more frequently between close relatives than more distant relatives. An earlier study observed young monozygotic (MZ), dizygotic (DZ) and virtual (VT) twins as they completed a 23-item tacit coordination task. A repeated measures MANOVA showed that TC varied significantly with the degree of genetic relatedness, consistent with expectations. *Materials and Methods:* The present study included 43 MZ twin pairs and 34 DZ twin pairs, ages 12–59 years. Twins completed a Tacit Coordination Questionnaire that was the same as the one given in the earlier study. They were asked to answer questions Individually and in a Coordination condition; the second condition was done to determine if co-twins would arrive at the same answer (non-negotiated consensus). Zygosity was assessed by a standard physical resemblance questionnaire, except in cases where DNA analysis had been performed. All twins were drawn from the southern California area, with the exception of 16 pairs from a Florida high school whose teacher was trained to administer the protocols. The primary analysis was a repeated measures MANOVA (General Linear Model) with one between-group factor: Zygosity (MZ, DZ); and two within-subject factors: Condition (Individual, Coordination) and Questions (Part I, Part II). Questions were included as a within-subjects factor to maintain comparability with the earlier study. Logistic regression analysis was also applied to identify specific classes of items that best distinguished between twin types in these studies. *Results:* A significant multivariate effect was found for Zygosity, $F(1, 75) = 17.98$, $p < .001$. As expected, MZ twins obtained more matched responses than DZ twins. Both Condition, $F(1, 75) = 50.54$, $p < .001$, and Questions, $F(1,75) = 37.39$, $p < .001$, showed significant multivariate effects. Scores were higher under the Coordination than the Individual condition, and higher for Part I than Part II questions. *Conclusion:* The present constructive replication generally confirmed the previous findings. It is possible that mutual awareness of non-negotiated matched choices may constitute a class of mechanisms by which close relatives develop and maintain close social relations.

IMPULSIVITY, DELINQUENCY AND SUBSTANCE ABUSE IN ADOLESCENCE – CAN COMMON GENETIC OR ENVIRONMENTAL FACTORS EXPLAIN WHY THESE TRAITS OFTEN CO-OCCUR?

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Introduction: Personality traits such as impulsivity or low self-control have in many studies been linked to antisocial behaviors (e.g., rule breaking, criminality) and substance abuse in adolescents. Yet the etiological nature of this co-occurrence is not well understood. The aim of the present study is to test different multivariate genetic models that may explain etiologic overlap between impulsivity, delinquency and symptoms of substance abuse in adolescence. *Materials and Methods:* Self-report questionnaire data was provided from a young sample of 15- to 18-year-old MZ ($n = 276$) and DZ twins ($n = 441$) participating in a large cohort study of twins born in Norway between 1988 and 1994. *Results:* Multivariate genetic modeling was used to ultimately test three different models: Cholesky Decomposition, Independent Pathway and Common Pathway, that may explain the etiologic overlap between the three phenotypes of interest: impulsivity, delinquency and symptoms of substance abuse. The best fitting model was an ACE common pathway model where the common genetic and environmental effects were mediated through a latent phenotype that represents the variance shared among the measured phenotypes. This latent phenotype, labeled externalizing, was moderately heritable. In addition, both shared environment and non-shared environment showed moderate effects

on the latent externalizing phenotype. The Common Pathway model also allows for additional effects that are specific to each observed phenotype. Both genetic and environmental factors accounted for distinctions among the phenotypes. *Conclusion:* These results support the presence of a general externalizing factor, showing evidence for both common and specific etiologic factors across externalizing traits.

ASSOCIATION BETWEEN HEIGHT AND METABOLIC RISK FACTORS OF CARDIOVASCULAR DISEASES IN JAPANESE AND FINNISH TWINS

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Introduction: Poor childhood living conditions followed by rapidly improved material conditions have been speculated to predispose to metabolic disorders in later life. Both Japan and Finland have experienced very rapid economic development after World War II, from being poor countries to becoming the most affluent societies in the world. This theory is thus well consistent with the high cardiovascular disease (CVD) incidence in Finland, but poorly explains why the CVD incidence is low in Japan. In this study we used adult height as an indicator of childhood living conditions and studied how it is associated with basic metabolic traits in Japanese and Finnish twins. *Materials and Methods:* Measured information from height and basic metabolic indicators was available from 160 complete twins pairs in Japan (all MZ, 74% females) and 217 complete twin pairs in Finland (all females, 47% DZ). The age range of participants in Japan was 21–88 years and in Finland 63–76 years. We first analyzed the association between height and the metabolic factors between individuals and within twin pairs discordant for height and the metabolic indicators using regression analysis. After that, using Cholesky decomposition we decomposed all statistically significant associations between height and the metabolic factors in the Finnish data with information from both MZ and DZ twins. *Results:* We found a statistically significant association between height and systolic blood pressure (r = -0.44 95% CI -0.85, -0.03) and marginally significant association between height and diastolic blood pressure (r = -0.18 95% CI -0.36, 0.01) in all Finnish twin pairs, whereas the associations between height and total cholesterol, HDL cholesterol and LDL cholesterol were weak and statistically non-significant. In Japan, none of these associations were statistically significant and we did not find statistically significant associations within discordant twin pairs in Japan or in Finland. When applying Cholesky decomposition, we found that the best model for the association between height and blood pressure was additive genetic/specific environment model with genetic correlation. Using this model, the additive genetic correlation, however, was only marginally statistically significant between height and systolic (rA = -0.13 95% CI -0.28, 0.02) and diastolic blood pressure (rA = -0.10 95% CI -0.24, 0.05). *Conclusion:* Although short stature has been found to be associated with higher CVD risk in several populations, we found only weak associations between height and the key metabolic risk factors of CVD in Japan and Finland. The moderate association between height and blood pressure in the Finnish population was due to common genetic factors. A study this association in other populations is warranted to to find out how universal this association is.

CODATWINS PROJECT: UNDERSTANDING MACRO-ENVIRONMENTAL VARIATION IN GENETIC AND ENVIRONMENTAL EFFECTS

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Introduction: 'Heritability estimates are not constant but are dependent on environment.' This is a basic tenet of twin studies and statistical genetics, but hardly anything is known on the environmental factors modifying the heritability estimates of even most simple traits. CODATwins project was established to analyze this issue in height and relative weight from early childhood to old age by utilizing twin data sets already collected. Further, we aim to analyze educational differences in height and weight and how smoking affects relative weight in adulthood in international context. High activity in twin cohorts all over the world in the recent decade has greatly improved the opportunity to analyze these issues through international collaboration. *Materials and Methods:* In autumn 2013 we contacted all twin cohorts in the world. The contact information of the cohorts was collected from several sources. The most important source was the special issue of *Twin Research & Human Genetics* (vol. 16, no. 1), and this was complemented from the information of INTR consortium participants and personal contacts. Together we were able to identify 74 twin cohorts from 30 countries in six continents. *Results:* Participation in the project has been very good, and the CODATwins database is already the largest twin data set in the world, including more than 100,000 twin pairs. More cohorts are expected to participate before the end of 2014. The latest status of the database will be presented. Issues related to contacting twin cohorts, working with data files, harmonizing variables and other issues important for international collaboration will be discussed. *Conclusion:* CODATwins is an example on the opportunities of international collaboration to answer research questions impossible to analyze using only one cohort. It also demonstrates the opportunities for extracting more information from well-studied traits by international collaboration. The scope of this project is limited to simple traits, but these experiences may be useful when planning further collaborative projects to analyze more complex issues.

GENETICS OF CARDIOVASCULAR DISEASES

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Introduction: Genetics of the metabolic risk factors of cardiovascular diseases (CVD) has attracted considerable scientific interest, but much less is known about the genetics of CVD risk itself. This is partly because of the heterogeneous nature of CVD but mainly because analyzing CVD incidence needs longitudinal data and much larger sample sizes than when analyzing metabolic traits. However, from the public health point of view, CVD risk is much more important outcome than its risk factors, and also for patients it would be informative to have an estimate of their genetic susceptibility of CVD risk. *Materials and Methods:* There are new models available to estimate the heritability of CVD incidence, using twin data when taking into account the censoring because of other causes of death. Genetic risk scores have also been developed based on the results of genome wide association analyses, and their predictive power for further CVD incidence and mortality have been tested. *Results:* Based on the results of the pooled data of Danish,

Finnish and Swedish twin cohorts, mortality from coronary heart disease and stroke shows moderate heritability. The latest unpublished results will be presented. These results will be discussed in the light of the latest genome wide association studies of CVD incidence. *Conclusion:* CVD mortality shows lower heritability than many of its metabolic risk factors, reflecting the heterogeneous nature of CVD risk. This may complicate the efforts to find candidate genes of CVD risk. However, these estimates are important, to give patients solid information about their genetically based risk of death from CVD. This can already be estimated based on the information on family history, and in the future genetic risk scores may improve these estimates. The knowledge of genetic susceptibility of CVD can be used to identify those persons for whom following healthy lifestyle would be especially important to avoid further CVD.

NON-RESPONSE BIAS FOR HEALTH STATISTICS IN THE VIETNAM ERA TWIN REGISTRY

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Introduction: Non-response can lead to bias when respondents are systematically different from non-respondents. We assessed the impact of non-response bias on estimates of prevalence, association, and heritability among members of the Vietnam Era Twin (VET) Registry who were recruited to Registry-wide surveys in 1985 and 2011. *Materials and Methods:* The VET Registry is a national sample of 14,738 U.S. male twins who served in the military during the Vietnam era (1964–1975). The VET Registry was assembled from military records and has served as a platform for physical and mental health research. An attempt to contact all twins was made in 1985; in total, 10,974 twins participated in a baseline survey for a response rate of 74.5%. In 2011, we conducted another registry-wide survey as part of long-term follow-up study of posttraumatic stress disorder (PTSD); in total, 7,562 participated in the follow-up study including 1,054 not reached in 1985. All VET Registry members have demographic and military service characteristics obtained from military records. The 2011 study was extensive and included 46 measures of physical and mental health including PTSD diagnosis by telephone interview using the Composite International Diagnostic Interview (CIDI). Initial analysis compared the 2011 physical and mental health characteristics among those who participated in both 1985/2011 studies ($n = 6{,}508$) and those who only participated in the 2011 study ($n = 1{,}054$). We then obtained estimates among all responders to the 2011 study and a subset who participated in both the 1985/2011 studies, longitudinal responders. We then estimated and compared disease prevalence, odds ratios or mean differences for the association with Vietnam service, and heritability across the groupings of all and longitudinal responders. *Results:* Veterans who only participated in the 2011 health survey reported significantly worse physical and mental health than those who participated in both the 1985/2011 studies ($p < .05$ in 40 out of 46 health conditions). Compared with all responders, longitudinal responders reported better health with an average of a 9.7% lower prevalence of mental and physical health conditions ($p < .001$). For example, the prevalence of PTSD was 11.0% in longitudinal responders and 12.7% in all responders, a relative difference of 15.4%. While there was a significant difference in association of Vietnam service with health conditions when comparing all with longitudinal responders ($p < .02$), the magnitude was modest: mean ratio of odds ratios was 0.97, 95%CI 0.95–0.99. For example, the association of Vietnam service with a diagnosis of current PTSD was estimated with an odds ratio of 2.1 in longitudinal responders and 1.9 in the all responders. Similarly, there was little difference in heritability estimates across the health conditions between all responders and longitudinal responders: mean difference was 0.037, 95%CI = 0.001–0.073. For example, the heritability for a diagnosis of PTSD was 0.35 in all responders and 0.39 in longitudinal responders. *Conclusion:* There was evidence of non-response bias in the VET Registry and this bias was most serious for estimating prevalence of physical and mental health conditions. The extent of bias may be more limited for estimates of association and heritability.

OPTIMAL TIMING FOR TERM DELIVERY OF TWIN PREGNANCIES: A NATIONAL POPULATION-BASED STUDY

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Introduction: Twin pregnancies comprise an increasing proportion of the total number of pregnancies in the United States. However, the optimal timing for delivery in twins to achieve optimal neonatal outcome remains controversial, based on limited results from clinical trials and particularly because of a national push to defer elective deliveries until at least 39 completed weeks' gestation. Our objective in this study was to examine the risk of adverse neonatal outcomes after twin delivery according to gestational age in a national population-based sample. *Materials and Methods:* The U.S. Natality Database from 2007–2010 was reviewed, with inclusion criteria being twin deliveries, gestational age between 37–42 weeks, and exclusion criteria being congenital anomalies, missing/incomplete data. As recently recommended, cases were subdivided by gestational age into early term (37–38 weeks), term (39–40 weeks) and late term (41–42 weeks) groups. Singleton pregnancies matched only by delivery time and location were selected as controls. Outcome variables included an a priori constructed composite score of neonatal complications, as well as low Apgar score, assisted ventilation, NICU admission, surfactant/antibiotic use, seizures, and birth injury. Logistic regression analysis was used to calculate adjusted odds ratios according to gestational age and plurality, using risk of singleton birth at term as reference. *Results:* A total of 220,169 term twin deliveries, essentially all that occurred in the United States over 4 years, and 270,540 singleton deliveries were identified. The risk of adverse neonatal outcomes for twins ranged from about two to over four times higher than for singletons as term gestational age advanced. For twins, the distribution of the risks of the composite of adverse neonatal outcomes was linear, being the lowest at early term and the highest at late term, rising nearly 2-fold, whereas the distribution for singletons was, as expected, U-shaped being lower at term compared to early and late term. *Conclusion:* Twins are at higher risk of suboptimal neonatal outcomes than singletons, but do substantially better when delivered at early term rather than term or late term. Though we could not separate cases for zygosity, this population-based study shows very large differences among the three term groups and so strongly suggests that as opposed to singleton delivery, twin delivery should not be deferred until 39 weeks' gestation.

CASE REPORT OF 143DAYS DELAYED DELIVERY OF THE SECOND TWIN AFTER THE MISCARRIAGE OF THE FIRST FETUS AT THE 16TH WEEK OF PREGNANCY

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Introduction: Delayed delivery of the second twin after the miscarriage of the first fetus is very rare. *Results:* We report a case of retention of the second twin after delivery of the first one at 16th week of pregnancy. The delay time was of 20 weeks 3 days (143 days). A 36-year-old, nulliparous woman conceived after in vitro fertilization and was found to have diamniotic-dichorionic twins. At 16 weeks 1 day, she presented with premature preterm rupture of the membranes of first twin. She delivered her first twin baby 3days after spontaneous rupture of the membrane.The newborn died on the first day of life due to prematurity. Emergency cervical cerclage was performed after first baby delivery at 16 weeks 3 days. and she received antibiotics and tocolytics. The second twin was successfully delivered vaginally at 36 weeks 6 days. A female infant (2,280 g) was delivered who did not need mechanical ventilation. *Conclusion:* Emergency cervical cerclage to postpone the delivery interval in premature dichorionic twin pregnancies can improve the life expectancy of the retained fetus.

CONDITIONED PAIN MODULATION IN UROLOGIC CHRONIC PELVIC PAIN: A MAPP RESEARCH NETWORK TWIN STUDY

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Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) is one of the urologic chronic pelvic pain syndromes. These syndromes include chronic pelvic pain with or without voiding symptoms such as urgency and frequency. Currently, no reproducible, consistent pathological findings, disease phenotypes, or other markers exist, although recent research has suggested dysfunction with the endogenous pain inhibitory system, referred to as conditioned pain modulation (CPM), in which 'pain inhibits pain'. Our goal was to replicate these results in a community-based sample of twins. *Materials and Methods:* We enrolled 14 monozygotic (MZ) and 9 dizygotic (DZ) female twin pairs discordant for IC/BPS as defined by a sensation of pain, pressure or discomfort, related to the bladder and/or pelvic region, associated with lower urinary tract symptoms and present for the majority of the time during the most recent 3 months. We also enrolled 14 MZ and 10 DZ healthy female control pairs. In addition, one each MZ and DZ pair was concordant for IC/BPS at the study visit. Healthy co-twins and control pairs reported no pain in the pelvic or bladder region or in more than one other region of the body, and no other current urologic symptoms. Due to the length of study visits and associated participant burden, the CPM protocol was made optional for participants and 39 out of 48 pairs completed it (19 discordant, 19 healthy, 1 IC/BPS concordant). The CPM protocol followed prior published reports in which a heat pain rating of 6 out of 10 was elicited from participants based on stimuli between 43°C and 49°C ('Pain6') applied to the dominant volar forearm by a heat thermode. The Pain6 stimulus was then repeated in the presence of a conditioning stimulus in which the opposite arm was placed in a water bath at 46.5°C and a second set of pain ratings obtained. The technicians were not blind to IC/BPS condition. Healthy CPM would be demonstrated by reduced pain ratings (i.e., negative mean values) in the presence of the conditioning stimulus. *Results:* Contrary to expectations, IC/BPS cases showed greater CPM (Mean = -0.90, SE = 0.26) compared to controls (Mean = -0.14, SE = 0.20) using GEE to account for correlated outcomes within twin pairs (B = .762, p = .02). We conducted a post-hoc analysis to evaluate if the pain rating for the conditioning stimulus contributed to the results. Although there was no difference between groups, putting the conditioning stimulus pain rating into the GEE model reduced the effect of case status (B = .544, p = .07) and was itself a significant predictor (B = -.184, p = .01) in the expected direction (higher pain rating, greater CPM). *Conclusion:* These results are not consistent with, in fact are opposite to, prior findings in IC/BPS suggesting problems with endogenous pain inhibition. However, some caution is warranted. First, this was a community-based, not clinic-based, sample and the results may not generalize to the typical urology patient. Second, although our method was based on published results, it was different from the method used in other IC/BPS research.

LEUKOCYTE TELOMERE LENGTH (LTL) IN UROLOGIC CHRONIC PELVIC PAIN: A MAPP RESEARCH NETWORK TWIN STUDY

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Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) is one of the urologic chronic pelvic pain syndromes (UCPPS). These syndromes include chronic pelvic pain with or without voiding symptoms such as urgency and frequency. No organ-specific disease has been conclusively identified for the disorders and there are significant comorbidities, including depression, which are relevant to a complete understanding of UCPPS. Currently, no reproducible, consistent pathological findings, or other markers exist, although systemic inflammation appears to be relevant to the disease process. Chronic inflammation can lead to critical changes in leukocyte telomere length (LTL), a recognized biomarker of cellular aging. Telomeres cap the ends of chromosomes and shorten with cell replication. Shortened telomeres may denote vulnerability to chronic pain; once present, chronic pain can then contribute to physiological mechanisms that accelerate telomere shortening. *Materials and Methods:* We enrolled 14 monozygotic (MZ) and 9 dizygotic (DZ) female twin pairs discordant for UCPPS defined by a sensation of pain, pressure or discomfort, related to the bladder and/or pelvic region, associated with lower urinary tract symptoms and present for the majority of the time during the most recent 3 months. We also enrolled 14 MZ and 10 DZ healthy control pairs. One additional MZ and DZ pair was concordant for UCPPS at the study visit. Healthy co-twins and control pairs reported no pain in the pelvic or bladder region or in more than one other region of the body, and no other current urologic symptoms. We established feasibility and preliminary results from the first 8 discordant MZ pairs to complete the protocol. Twins underwent an experimental bladder pain protocol to induce IC/BPS-like symptoms by drinking 350–500 ml of water about 40 minutes prior to undergoing brain magnetic resonance imaging (MRI). Using a 10-point scale, they rated their pain after the scan but before voiding. LTL was measured by quantitative PCR. The amount of telomeric DNA was divided by the amount of control-gene DNA, producing the standard T/S ratio outcome variable. Depression was measured by the Hospital Anxiety and Depression Scale (HADS). The same methods are currently being deployed for the remaining pairs. *Results:* In 5 of 8 pairs, LTL

was shorter in the UCPPS twins than in healthy co-twins. Mean differences were in the hypothesized direction but were not statistically significant. Shorter telomeres were positively associated with pain ratings during the bladder instillation procedure (B = -0.029, p = .01) and with levels of HADS depression as measured by the (B = -11.052, $p < .0005$). Complete data from all pairs will be available for the ISTS meeting. *Conclusion:* Chronic pain can affect LTL by pro-inflammatory stress processes. Our model proposes that shorter telomeres, as a function of genetics and environmental exposures such as stress, denote a vulnerability to chronic pain, which contributes to physical and psychological processes relevant to telomere shortening. In combination with other ongoing research, this study may link epigenetic modification, systemic inflammation, LTL, and pain severity in patients with UCPPS.

DNA METHYLATION IN UROLOGIC CHRONIC PELVIC PAIN: A MAPP RESEARCH NETWORK TWIN STUDY

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Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) is one of the urologic chronic pelvic pain syndromes (UCPPS). These syndromes include chronic pelvic pain with or without voiding symptoms such as urgency and frequency. No organ-specific disease has been conclusively identified for either disorder and there are significant comorbidities, including depression, which are relevant to a complete understanding of UCPPS. Currently, no reproducible, consistent pathological findings, disease phenotypes, or other markers exist. DNA methylation, a process by which gene expression is altered without altering DNA structure, may be related to key aspects of chronic pain, including regulation of peripheral inflammation and expression of genes related to pain processing. *Materials and Methods:* We enrolled 14 monozygotic (MZ) and 9 dizygotic (DZ) female twin pairs discordant for UCPPS defined by a sensation of pain, pressure or discomfort, related to the bladder and/or pelvic region, associated with lower urinary tract symptoms and present for the majority of the time during the most recent 3 months. We also enrolled 14 MZ and 10 DZ healthy control pairs. One additional MZ and DZ pair was concordant for IC/BPS at the study visit. Healthy co-twins and control pairs reported no pain in the pelvic or bladder region or in more than one other region of the body, and no other current urologic symptoms. We established feasibility and preliminary results from 8 discordant MZ pairs and 4 healthy MZ pairs. DNA methylation levels of peripheral blood cells were assessed by using the Illumina HumanMethylation450 Bead Chip. Samples from each of the 24 participants were randomly assigned to one of 2 chips for analysis. The same methods are currently being deployed for the remaining pairs. *Results:* Given our small sample, methylation analysis sites was restricted to loci in the Algynomics Pain Research Panel v 2.0. Evaluation of the Manhattan Plot revealed a stacked peak of increasingly significant differentially methylated regions (DMRs) in the correlated CpG regions in Chromosome 6. No individual loci were significant after correcting for multiple comparisons, likely because of low power for dichotomous comparisons in the feasibility sample. After evaluating DMRs as a function of case status, we investigated whether methylation was related to depression (Hospital Anxiety and Depression Scale; HADS). The Manhattan Plot for methylation as a function of depression revealed a similar stacked peak in Chromosome 6 and a statistically significant relationship with PRKAR1B which is involved in the regulation of lipid and glucose metabolism and is a component of the signal transduction mechanism of certain G protein-coupled receptors. Complete data from all pairs will be available for the ISTS meeting. *Conclusion:* This research could advance our understanding of UCPPS by suggesting epigenetic mechanisms that account for UCPPS in the absence of other noxious stimuli and that link UCPPS with depression. Unlike most biomarkers examined to date (e.g., urine proteins which can wax and wane in response to many factors) epigenetic modifications could illuminate the biological mechanism responsible for the transition from acute to chronic pain while serving as a target for novel therapies.

THE GENETIC LANDSCAPE OF CANNABIS USE: A META-ANALYSIS INCLUDING OVER 27,000 SUBJECTS

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Introduction: Cannabis is the most widely produced and consumed illicit drug worldwide. Previous research has demonstrated the adverse effects of cannabis use. Cannabis use may lead to abuse or dependence; subsequently causing physical, psychological and social problems. The International Cannabis Consortium (ICC) was created to combine results of multiple GWA studies in order to identify genetic variants underlying individual differences in cannabis use phenotypes. *Materials and Methods:* We performed a meta-analysis of 27,788 GWA samples from 12 samples collected in Europe, the US and Australia. Lifetime cannabis use (i.e., never/ever used cannabis) ranged from 1.26% to 91.6% with a median of 46.0%. Participating groups performed their own quality control. Imputation and GWA analysis were performed according to a standardized protocol. All imputations were based on the same reference panel (1000 genomes phase 1 European (EUR)). All GWA analyses were based on dosage data and corrected for age, sex, and birth cohort effects and population stratification by controlling for ancestry PCs. Additionally, we performed gene-based tests of association. *Results:* Although the QQ-plot clearly indicated enrichment of nominally significant findings, no genome-wide significant hits were identified. The statistically most significant marker was located on chromosome 12 (12:30479358) with a p-value = 8.6*10-8. This polymorphism is located in an intergenic region about 30 kb from transmembrane and tetratricopeptide repeat containing 1 (TMTC1) and 30kb from Importin 8 (IPO8). Among the 23,523 genes tested, none reached genome-wide significance following FDR correction. The lowest p-value from the gene-based test was found for Gamma-Aminobutyric Acid (GABA) A Receptor, Rho 3 (GABRR3) (p = 9.46*10-5). We have access to two independent replication samples, including another ~3500 subjects in which we aim to test for replication of the top 10 SNPs. *Conclusion:* We present preliminary results of the world's largest meta-analysis of cannabis use to date. The QQ-plot of this meta-analysis indicated significant enrichment of nominally significant findings. One polymorphism approached genome-wide significance which may be an interesting candidate for future replication studies. This SNP is located near the gene TMTC1, previously associated with weight-related phenotypes. Because the reward system in the brain plays a role both in eating behaviors and substance use, this gene is therefore an interesting candidate for future studies. In this regard, the top-result in the gene-based tests was GABBR3. Previous research suggests that

GABA plays a role in addictive behaviors through its involvement in the reward pathway, and although no significant association was detected, the role of this gene in cannabis use should be further investigated.

THE SRI LANKAN TWIN REGISTRY

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Introduction: Twin research helps to determine the degree to which traits and disorders are heritable. Most such studies use volunteer registers and are from North America, Europe and Australasia. Population-based registers are rare even in the West. The Sri Lankan Twin Registry (SLTR) is the first of its kind in a low and middle income country. *Materials and Methods:* It was proposed by the first author and founded in 1997, and launched at the 110th annual scientific sessions of the SLMA, initially as an island-wide volunteer cohort through media publicity. It was later extended to a population-based cohort (Colombo district) with a strategic collaboration between the Institute for Research and Development and the Institute of Psychiatry, King's College, London, with competitive charitable funding. *Results:* A volunteer cohort comprises 14,130 twins (7,065 pairs) and a population cohort 19,040 (9,520 pairs). Feasibility studies (five papers), were followed by The Colombo Twin and Singleton Study (CoTaSS 1) exploring the prevalence and heritability of a range of psychiatric disorders and gene-environment interplay (seven papers) and establishment of a genetic laboratory. Second wave follow-up (CoTaSS 2) on depression and metabolic syndrome explores the prevalence and interrelationship of a number of key cardiovascular and metabolic risk markers and establishment of a bio-bank (DNA and serum). *Conclusion:* In the context of scarcity of research capacity in LAMIC, the SLTR has showcased how successful North-South partnerships can overcome barriers to minimize the 10/90 divide, leading to influential high quality research and publications in high impact journals.

CHANGES IN DNA METHYLATION IN RHEUMATOID ARTHRITIS AND THE EFFECT OF SMOKING, ANTI-CCP AND TREATMENT: AN EPIGENOME WIDE ASSOCIATION STUDY IN MONOZYGOTIC RA DISCORDANT TWIN PAIRS

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Introduction: In rheumatoid arthritis (RA) global DNA hypomethylation has been reported in both peripheral blood mononuclear cells (PBMC) and rheumatoid arthritis synovial fibroblasts (RASF). Several studies have focused on the methylation of candidate loci in PBMC from RA patients. Few studies have been done at the epigenomic level. Systematic epigenomic equivalents of genome-wide association studies (GWAS) for DNA methylation are now available. The latest epigenome wide association study (EWAS) identified more than 50,000 differentially methylated positions (DMPS) in peripheral blood from treatment naïve anti-CCP positive patients. Monozygotic (MZ) twin pairs discordant for disease are genetically matched enabling the identification of differential DNA methylation elicited by environmental exposure and intrinsic effectors. One previous EWAS on 5 MZ discordant pairs found no significant changes in PBMC. *Materials and Methods:* The study comprised 28 MZ RA discordant twin pairs. Genomic DNA from peripheral blood was analyzed using the Illumina 450K methylation assay according to the manufacturer's instructions. Since our analysis was based on whole blood, we adjusted cell-type compostion and further downstream analyses were based on this adjusted dataset. Smoking may lead to extensive genome-wide changes in DNA methylation. Smoking is associated with anti-CCP positive RA in particular and there is increasing evidence to suggest that anti-CCP positive RA is an etiologically distinct subset of RA. Therefore, smoking and anti-CCP were included as covariates. Methotrexate may elicit profound effects on DNA methylation. Therefore current treatment with DMARD was also included as a covariate. Differentially methylated positions (DMP): We fitted a linear regression model predicting the mean fold change in DNA methylation between the RA and the non-RA co-twin from RA discordant MZ twin pairs at each CpG site adjusting for age, sex, ever-smoking, anti-CCP and current DMARD treatment. Differentially methylated regions (DMR): It has been demonstrated that methylation levels are strongly correlated across the genome and functionally relevant findings have been generally associated with genomic regions rather than single CpGs. We used the 'Bump Hunting' method, which assumes that the locus-specific estimates of the regression coeffcients (βs) are smooth along the strand of DNA and applies the loess smoothing technique to smooth βs within a predefined region (300 base pairs in our analysis). The 99th percentile of the smoothed βs was calculated to obtain upper and lower tresholds to define hyper- and hypo-methylated DMRs. For each DMR identified, bumphunter calculates a sum statistic used to rank all the DMRS. *Results:* Differentially methylated positions: After adjustment for cell-composition we did not find any FDR adjusted significant DMPS for RA or any of the covariates including smoking. Differentially methylated regions (Bump hunting): We identified several DMRs associated with RA in the regulatory sites of several genes. Among the top ranked DMRs, one encoded a gene which has previously been shown to be upregulated in peripheral blood from RA patients and the expression was positively correlated with the levels of serum MMP3, a matrix metalloproteinase involved in cartilage destruction and bone erosions. Another DMR was nearby, a gene encoding a 56-kDa protein structurally related to the 52-kDa Ro/SSA antigen, and represents a new member of the SS family of autoantigens detected in Sjøgrens Syndrome and SLE. Smoking caused a DMR in RA twins associated with two genes clustered in the class III HLA region that has been linked with myositis, SLE and type 1 diabetes and two other genes associated with circulating resistin, a hormone that has been associated with insulin resistance, inflammation, NIDDM and cardiovascular disease. Treatment revealed a DMR in RA twins in the promoter region of the same two genes in the class III HLA region associated with smoking but the methylation pattern was reversed indicating that DMARD treatment may abolish the methylation effect of smoking. *Conclusion:* We measured more than 485,000 CpG loci across a diverse set of functionally relevant genomic regions using the Infinium HumanMethylation450 BeadChip. We did not find significant genome-wide differentially methylated positions but identified several differentially methylated regions (DMRs) using a bump hunting approach. The DMRs identified in this study emphasize the relevance of some genes that have already been identified as candidates in the pathogenesis of RA, inflammation and other autoimmune diseases. Our study also suggests a possible counteracting effect of DMARD treatment on smoking-related hypomethylation in RA.

A REVIEW OF INTRAUTERINE DEATHS IN TWIN PREGNANCIES OCCURING IN CORK UNIVERSITY MATERNITY HOSPITAL BETWEEN 2009 AND 2012

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Introduction: Twin births currently represent 1.8% of all births in Ireland. The rate of multiple births are increasing due to the combined effect of a rise in maternal age and increased use of assisted reproductive technologies. These pregnancies are at a greater risk for adverse perinatal outcomes compared to their singleton counterparts. Early diagnosis of amnionicity and chorionicity is essential as monochorionic pregnancies have a 3- to 5-fold increased risk of fetal morbidity and mortality compared to dichorionic pregnancies. Our aim was to establish the intrauterine death (IUD) rate beyond 12 weeks gestation among twin pregnancies at Cork University Maternity Hospital (CUMH) between 2009 and 2012. We also aimed to identify the etiology of the loss in terms of chorionicity, gestation, and the underlying cause of the loss. *Materials and Methods:* Using the CUMH Twin Pregnancy and Perinatal Mortality Registers, we identified all cases of single or double fetal loss beyond 12 weeks gestation. Individual charts were then reviewed. *Results:* During this 4-year period, 692 twin pregnancies (572 DCDA, 117 MCDA, 2 MCMA, 1 conjoined twins) were managed in CUMH. In total, 22 twin pregnancies suffered single or double loss beyond 12 weeks gestation. Two pregnancies were excluded from the review due to the lack of available documentation.Out of these pregnancies, there were 9 single and 10 double IUDs and 1 double stillbirth. In terms of chorionicity and amnionicity, 8 DCDA, 10 MCDA and 2 MCMA pregnancies were affected. Among the DCDA pregnancies, the mean gestational age of the loss was $23 + 1$ weeks gestation in single loss, $18 + 2$ weeks gestation for twin 1 and $19 + 6$ weeks gestation for twin 2 in double loss. In MCDA prgenancies, the mean gestational age of the loss was $22 + 6$ weeks gestation in single loss and $21 + 2$ in double loss. *Conclusion:* From 2009 to 2012, in 3.17% of twin pregnancies there was loss of one or both twins after 12 weeks gestation. In DCDA twins, it represents a loss rate of 1.39% (0.87% single loss rate and 0.52% double loss rate). In MCDA pregnancies the overall loss rate beyond 12 weeks gestation was 8.54% (3.42% single loss rate and 5.23% double loss rate). Both of the MCMA pregnancies managened in CUMH during this 4-year period resulted in double twin loss (100%). The stillbirth rate was 7.98 per 1,000 twin births.

PREVALENCE OF CONGENITAL HEART DISEASE IN TWIN PREGNANCIES IN CORK UNIVERSITY MATERNITY HOSPITAL BETWEEN 2009 AND 2013

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Introduction: Congenital heart disease (CHD) is the most common congenital abnormality in neonates, with moderate or severe anomalies occurring in about 6 per 1,000 live births. Several studies suggest that twin pregnancies are at a higher risk for CHD compared to their singleton counterparts. In monochorionic twins a 9-fold increased risk has been shown, especially in cases where the pregnancy is complicated with twin-to-twin transfusion syndrome (13-fold increased risk). Cork University Maternity Hospital (CUMH) is one of the biggest maternity hospitals in Ireland, with a well-structured care pathway and consultant delivered service for women with twin pregnancies. An early scan is performed in all cases to establish chorionicity and amnionicity. Women undergo a detailed anomaly scan between 19 and 22 weeks of gestation. Depending on the chorionicity, fortnightly or 4-weekly ultrasound assessments for fetal growth, presentation and amniotic fluid index are performed. *Materials and Methods:* Our aim was to establish the prevalence rate of moderate and severe CHD in twin pregnancies and to determine what proportion of these cases was antenatally diagnosed. We used the following hospital databases to identify twin pregnancies affected with CHD: Twin Pregnancy Register, Perinatal Mortality Register, Fetal Medicine Database, Neonatal Database; and examined discharge summaries and transfer letters from the neonatal unit. Individual maternal and neonatal charts were then reviewed. We excluded all cases with minor CHD, such as patient ductus arteriosus. *Results:* During this 5-year period, 861 twin pregnancies (714 DCDA, 141 MCDA, 4 MCMA, 2 conjoined twin) were managed in CUMH. In total, 14 cases were indentified where one fetus was affected by CHD (10 DCDA, 4 MCDA), and one case of conjoined twins where both fetuses were affected. The proportions of the different types of CHD among our cases were the following: 3 hypoplastic left heart syndrome (HLHS), 3 atrioventricular septal defect (AVSD), 2 ventricular septal defect (VSD), 1 coarctation of the aorta, 2 tetralogy of fallott (TOF), 1 transposition of the great arteries (TGA), 2 unclassified (1 complex heart abnormality, 1 hypertrophy with pericardial effusion). Eight of the patients had an antenatal diagnosis of CHD. The mean gestational age of diagnosis was $21 + 1$ weeks. *Conclusion:* From 2009 to 2013, the prevalence of CHD among twin pregnancies in CUMH was 1.5%. This represents a prevalence rate of 1.4%, 3% and 50% in DCDA, MCDA and conjoint twin pairs respectively. 54% of our patients had an antenatal diagnosis of CHD.

TWIN CHORIONICITY AND THE RISK OF PREECLAMPSIA

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Introduction: Twin pregnancy is associated with an increased risk of preeclampsia. However, it is uncertain how chorionicity of twin pregnancy affects this risk. Recent studies indicate a possible higher risk of preeclampsia in dichorionic pregnancies (DCP). The main objective of the study was to verify if chorionicity may affect the risk of preeclampsia and additionally analyze the outcome of preeclampsia-affected pregnancies. *Materials and Methods:* It was a retrospective analysis of selected patients in twin gestations who gave birth at the 1st Department of Obstetrics and Gynaecology, Medical University of Warsaw, between 2007 and 2013. There were 189 women with dichorionic pregnancies and 60 women with monochorionic pregnancies included in the study. The following parameters were analyzed: maternal characteristics, hypertension history, the presence of chronic renal diseases, fetal intrauterine growth restriction, systolic and diastolic blood pressure, proteinuria, distal oedemas, time of hypertension onset, liver enzymes level, neurological complications, treatment of hypertension, cesarean section rate with indications, newborns' birth weight, Apgar score at 1st and 5th min. The data were analyzed with SAS software, with elements of multiple factor analysis and with p-value $<.05$ considered significant. *Results:* Patients with DCP had significantly higher chances to develop preeclampsia (OR = 5.26; 95%CI 1.17–32.93; $p = .013$) than MCP. Although it was confirmed that DCP mostly increased

chances to develop mild preeclampsia (OR = 4.71; 95%CI 1.04–29.64; $p = .024$), its association with severe preeclampsia was not confirmed. However, DCP were not more likely to develop gestational hypertension in comparison to MCP (8.99% vs. 8.33%; $p = .86$). 80.7% of preeclampsia-affected pregnancies developed mild hypertension, while 9.7% moderate. In 38.7% of gestations complicated by preeclampsia, proteinuria exceeded 1.0g/day. Pregnancies affected by preeclampsia did not differ in the rate of IUGR and thrombocytopenia from the not-affected pregnancies. On the other hand, MCP were more likely to involve PROM (OR = 3.93; 95%CI 1.71–9.07; $p = .001$), had stronger association with PTB (OR = 1.89; 95%CI 0.96–3.83; $p = .05$) and Apgar score of 1–3 points (OR = 3.65; 95%CI 1.37–9.72; $p = .007$). *Conclusion:* Increased chorionicity does not increase of the risk of isolated gestational hypertension. However, DCP is a stronger risk factor for preeclampsia than MCP.

SELECTIVE GROWTH RESTRICTION IN MULITPLE PREGNANCY: IS THERE A OPTIMAL TIME FOR DELIVERY?

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Introduction: Intrauterine growth restriction (IUGR) remains one of the major problems in obstetrics as it contributes disproportionately to neonatal mortality and morbidity. In dichorionic twins, selective fetocide of one severe IUGR fetus in midtrimester twin pregnancies complicated by severe preeclampsia may abort the disease process and prolong the pregnancy. For monochorionic twins, the finding of abnormal umbilical artery dopplers may be a manifestation of the transmission of the bidirectional waveforms of arterio-arterial anastomosis, but has been shown to be associated with an increased risk of intrauterine death in the growth-restricted fetus and brain damage in the larger fetus. In this case series, we summarize the diagnostic and management dilemmas associated with selective IUGR in monochorionic and dichorionic pregnancies with emphasis on best practice recommendations. *Materials and Methods:* Multiple pregnancies with IUGR of 1 twin were retrieved from the Singapore General Hospital Department of O & G ultrasound database. Serial growth and Doppler scans were reviewed. Delivery details and neonatal outcomes were retrieved from the Labour Ward database and case notes review. *Results:* There were two sets of triplets, two sets of monochorionic (MC) twins and one set of dichorionic (DC) twins, all with one severely growth restricted fetus and delivered by cesarean section between 27 and 34 weeks gestation. Patient A was delivered at 27 weeks when Triplet A (MC pair of DCTA) showed reversal of 'a' wave of the ductus venosus with neonatal death on day 3. Patient B delivered at 34 weeks for IUGR of Triplet C (TCTA) with good outcomes. Patient C delivered at 29 weeks for reversed end diastolic flow of umbilical artery of Twin B (MC), complicated by neonatal morbidities. Patient D was delivered at 30 weeks for Gratacos type III sIUGR with intermittently absent umbilical artery end-diastolic flow of IUGR Twin (MC), with placenta histology showing velamentous cord insertion IUGR Twin. Patient E (DC) was delivered at 27 weeks for maternal severe pre-eclampsia resulting in stillbirth of IUGR Twin. *Conclusion:* More evidence is accumulating to show that fetal Doppler changes of the ductus venosus and umbilical vein are good surrogate markers for fetal acidemia. The timing of delivery of the preterm growth-restricted fetus in a twin/triplet pregnancy remains controversial. Intrauterine growth restriction with intermittent absent or reversed end diastolic flow in the umbilical artery of monochorionic twins poses difficulties in assessment.

DIGESTIVE SYMPTOMS ARE INFLUENCED BY GENETIC AND FAMILY ENVIRONMENTAL FACTORS OF DEPRESSIVE SYMPTOMS

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Introduction: Previous studies have reported an association between digestive symptoms and depressive symptoms. However, it is unclear how genetic and environmental factors influence the association between digestive symptoms and depressive symptoms. The aim of present study was to investigate the association between digestive symptoms and depressive symptoms with consideration for genetic and environmental factors using genetically informative sample of twins. *Materials and Methods:* We recruited 188 monozygotic twin pairs (female: 136 pairs, male: 52 pairs) aged 20 years or over at Osaka University Center for Twin Research. Digestive symptoms and depressive symptoms were measured by subscales of Cornell Medical Index — Health Questionnaire. In a generalized linear mixed model (GLMM), we used scores of digestive symptoms as an outcome, age and medical histories of digestive diseases as potential confounders, difference scores of depressive symptoms within a twin pair and mean scores of depressive symptoms within a twin pair as predictors. The coefficient of the mean scores of depressive symptoms within a twin pair represents effects of factors shared by a twin pair such as genetic and environmental factors. On the other hand, the coefficient of difference scores of depressive symptoms within a twin pair represents effects of factors independent of confounding by factors shared within a twin pair. *Results:* In females and males, there were significant associations between digestive symptoms and mean scores of depressive symptoms. On the other hand, there were not significant associations between digestive symptoms and difference scores of depressive symptoms. *Conclusion:* This study reveal that digestive symptoms are influenced by genetic and family environmental factors of depressive symptoms.

RELATIONSHIP BETWEEN METABOLIC SYNDROME AND BRESLOW'S 7 HEALTH PRACTICE INDEX WITHOUT GENETIC FACTORS: A STUDY OF JAPANESE ADULT TWINS.

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Introduction: The prevalence of metabolic syndrome (MetS) has increased worldwide and it is associated with an increased risk of both diabetes and cardiovascular disease. Several previous studies have indicated that people developed MetS because of daily habits such as diet and exercise. However, these studies involved a general population without taking into effect genetic factors. With these factors not accounted for, it is impossible to get accurate results in terms of the relationship of MetS and daily habits. In this study, we investigated the relationship between MetS and lifestyle, using a twin study method that can be used to remove the confounding genetic factors. *Materials and Methods:* Among twin pairs registered at Center for Twin Research, Osaka University Graduate School of Medicine, 442 individuals participated in the health examination. Breslow's 7 health practice index (BHPI) was used to measure lifestyle. MetS

has defined five components (waist circumference, blood pressure, HDL cholesterol, triglycerides, fasting blood sugar). To investigate the relationship between MetS and lifestyle, we used generalized estimating equations (GEE), which control for clustering of twins within a pair. To assess the genetic and environmental factors, we used a general linear mixed model (GLMM), which provides a useful statistical approach for the regression analysis of data from co-twin control studies, with continuous outcome measures. In the study, BHPI was divided into two groups. It was classified that the good health group was BHPI ≥ 4. The other group was BHPI <4. *Results:* We included 324 (monozygotic twins: males = 102, females = 222) individuals in the analyses. In the GEE analyses, the good health group's male waist circumference and female HDL cholesterol had a significant association with BHPI. However, in GLMM analyses, male waist circumference was not associated with BHPI, but female HDL cholesterol was significantly related to BHPI. *Conclusion:* In males, common genetic factors influence the relationship between waist circumference and BPHI. Our finding suggests that HDL cholesterol was significantly associated with BHPI, when removing genetic factors in females. Thus, there is a possibility that desirable health habits improve HDL cholesterol, independent of genetic factors.

GENETIC EFFECTS ON THYROID GLAND SIZE IN HUNGARIAN TWINS

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Introduction: Decreased thyroid volume has been related to increased prevalence of thyroid cancer; however, genetic effects on thyroid gland size has not been determinated in a Hungarian cohort. *Materials and Methods:* 114 Hungarian adult twin pairs (69 monozygotic, 45 dizygotic) with or without known thyroid disorders underwent thyroid ultrasound. Thickness of the thyroid isthmus was measured at the thickest portion of the gland in the midline using electronic calipers at the time of scanning. Volume of the thyroid lobe was computed according to the following formula: thyroid height*width*depth* correction factor (0.63). *Results:* Age-, sex-, body mass index- and smoking-adjusted heritability of the thickness of thyroid isthmus was 50% (95% confidence interval [CI], 35 to 66%). Neither left nor right thyroid volume showed additive genetic effects, but shared environments were 68% (95% CI, 48 to 80%) and 79% (95% CI, 72 to 87%), respectively. Magnitudes of monozygotic and dizygotic co-twin correlations were not substantially impacted by the correction of covariates of body mass index and smoking. Unshared environmental effects showed a moderate influence on dependent parameters (24–50%). *Conclusion:* Our analysis did not support the heritability of thyroid volumes in a general twin population: the greatest part of variance was explained by shared environmental components, emphasizing the importance of common health and environmental interventions (e.g., intrauterine effects, regional nutrition habits, iodine supply) for primary prevention. In contrast, thickness of thyroid isthmus was moderately genetically influenced. Modifiable, unshared environment effects (e.g., smoking, body mass index, nutrition habits, alcohol consumption) had a moderate role. These factors can be eliminated/regulated in order to prevent the development of thyroid cancer.

HERITABILITY OF ABDOMINAL AORTIC DIAMETER: A HUNGARIAN TWIN STUDY

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Introduction: Various etiologies have been described for abdominal aortic aneurysm (AAA) development. Although AAA is thought to have a complex genetic and environmental background, the exact magnitude of these effects is still unclear on aortic dilation. Therefore, we aimed to assess the heritable, shared and unshared environmental effects on the diameter of abdominal aorta in a specific Hungarian population. *Materials and Methods:* 114 adult (69 monozygotic, 45 same-sex dizygotic) twin pairs (mean age 43.6 ± 16.3 years) recruited from the Hungarian Twin Registry underwent abdominal ultrasound with Esaote MyLab 70X ultrasound machine with curved array transducer to visualize the abdominal aorta below the level of the origin of renal arteries and 1–3 cm above the bifurcation. The largest aortic diameter was measured by electronic calipers at the time of scanning. *Results:* Age- and sex-adjusted heritability of the diameter of abdominal aorta under the level of the origin of the renal arteries was 40% (95% confidence interval [CI], 14 to 67%) and 55% above the aortic bifurcation (95% CI, 45 to 70%). None of the aortic diameters showed common environmental effects, but unshared environmental effects were responsible for 60% and 45% of the traits, respectively. *Conclusion:* Our analysis is the first to document the moderate heritability and its segment-specific difference of abdominal aortic diameter, suggesting a potential genetic determination of aortic dilation. Further studies should confirm whether high-risk individuals for aortic dilation could potentially benefit from a screening strategy. The moderate part of variance was explained by unshared environmental components, emphasizing the importance of lifestyle factors in primary prevention.

TWIN STUDIES AND REGISTRIES IN CENTRAL EASTERN EUROPE

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Introduction: A limited number of twin studies and registries exist in Central Eastern Europe (CEE). We aimed to collect the scientific activities related to twin studies in this region. *Materials and Methods:* PubMed and internet searches were performed to collect data concerning twin studies, registries and clubs in CEE countries. *Results:* Twin clubs, mainly consisting of young twins, have been found in Kosice, Slovakia and in some Czech cities (Prague, Ostrava and Plzen). In Poland, there are some sporadic research articles on twins, and a twins' festival is organised intermittently in Szczecin. In Croatia, there is a Zagreb twin cohort, with some publications in twin studies. A Croatian twin festival was organised in Omis in 2007 and 2008. In Hungary, we have a twin registry and we have published numerous twin studies. In addition, three twin festivals are organised in Hungary on a regular basis. No other twin registries or activities have been identified in other CEE countries. *Conclusion:* There is a lack of twin registries and clubs in most Central Eastern European countries.

TWIN STUDIES IN HUNGARY

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Introduction: Twin studies in Hungary date back to the 1970s on the basis of three different databases: the Budapest Twin Registry, the Hungarian Congenital Abnormality Registry and a voluntary registry. In the mid-2000s, we reignited the Hungarian Twin Registry with the help of Júlia Métneki and Levente Littvay. *Materials and Methods:* We aimed to summarize the most important findings of Hungarian twin studies, reviewing the literature. *Results:* Studies of Júlia Métneki and Andrew Czeizel mainly focused on various congenital abnormalities, the effect of contraceptive pills and folic acid on the frequency of twin pregnancies, as well as psychosexual and alcohol consumptional behaviors. Since the foundation of the Hungarian Twin Registry, numerous articles have been published in various topics, mainly related to cardiovascular and respiratory disorders. Although our registry is still small, it is constantly growing, and currently includes 650 twin pairs or multiplets. The number of researchers who want to collaborate with us is growing, and the interest in twin studies in Hungary is increasing in various scientific fields. *Conclusion:* In our opinion, Hungarian twin studies have been successful, and the increasing interest in our registry and the international support from other twin registries can further strengthen our activities.

PERINATAL AND NEURO-DEVELOPMENTAL OUTCOME OF TRIPLETS: A POPULATION-BASED APPROACH

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Introduction: Triplets appear to face more risks than singletons and twins, both in health and psychological outcomes. One needs unbiased quality data (not only voluntary based) to really estimate the impact of these risks in triplet pregnancies. *Materials and Methods:* From 1986 to December 1995, the East Flanders Prospective Twins Survey recorded a total of 85 triplet maternities. Only the deliveries in which one of the children weighed more than 500 g or, if birth weight was unknown, the gestational age was greater than or equal to 22 weeks, were considered. These numbers represent the near totality of triplets born in East Flanders during this time period. At the time of testing, the children were between 7 and 16 years old. All triplet families were contacted. Neuro-developmental outcome was assessed by the Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Child Behaviour CheckList (CBCL). A structured questionnaire was filled in by the parents to assess socio-economic status of the parents, school attendance of the children and familial history of mental retardation. *Results:* The perinatal mortality was high: in 5 sets (6%) all children, in 5 sets (6%) 2 children and in 15 sets (18%) 1 child. Of the remaining 80 triplet families, 19 families could not be retraced and 9 refused to fully participate, so only a short questionnaire was taken. Finally, 140 children from 52 triplet sets participated in the study. Of these, 19 children (14%) were from a spontaneous pregnancy, 73 (52%) were the result of artificial ovulation induction only, and 48 children (34%) were associated with assisted reproduction techniques (ART). Ten children (7%) from 8 triplet sets had an IQ lower than 80 (borderline intellectual functioning and mild mental retardation), which is higher than the expected frequency of 2% ($p < .01$). All of these children were the result of artificial reproduction techniques. Three children had cerebral palsy. Comparison of the birth weight and gestational age of the children with an IQ <80 and others show that lower gestational age (31.9 vs. 34.7 weeks) and lower birth weight (1619 g vs. 2056 g) are the main risk factors for a lower IQ ($p < .001$). There was no influence of sex and birth rank. Mothers of iatrogenic triplets had a higher educational level than mothers of spontaneous triplets. Although the non-participants were representative for gender, zygosity and origin of the pregnancy, they had a significantly lower birth weight and gestational age than the participants (1623 g vs. 2013 g in first-born triplets; 32.5 vs. 34.2 weeks) and their mothers had a lower educational level. *Conclusion:* In addition to an increased risk of mortality, triplets have higher rates of borderline intellectual functioning, mild mental retardation and cerebral palsy.

SENSE OF COHERENCE AND SUBJECTIVE WELLBEING IN A MIDDLE-AGED POPULATION

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Objective: Sense of coherence (SOC) is a global perceptual predisposition in responding to life stress, and it is said to be more likely to flexibly adopt adaptive strategies. Subjective wellbeings are well known to be highly correlated with physical and psychological wellbeings. However, the association between sense of coherence and subjective wellbeing has not been well investigated, especially in the middle-aged and older population. Thus, we examined this association in people aged 40–60 years and 60+ years. *Materials and Methods:* A self-reported questionnaire survey was conducted for 600 subjects aged 40 to 90 years in 2010. The questionnaires included subjective wellbeing, SOC, Instrumental Activity of Daily Living (IADL, assessed using Tokyo Metropolitan Institute of Gerontology Index of Competence), economic satisfaction, disease status, and chronic pain. Data was analyzed by using multiple regression analysis. *Results:* SOC was significantly associated with subjective wellbeing in the middle-aged population (aged 40–60 years). In contrast, SOC was not a significant predictive factor in the older population (aged 60+ years). Moreover, in the middle-aged population, chronic pain, opportunity to go out and IADL were associated with subjective wellbeing (adjusted $R^2 = 0.30$). Conversely, in the older population, disease status was strongly associated with subjective wellbeing (adjusted $R^2 = 0.23$). *Conclusion:* It was already proved that a SOC score was what will progress by adolescence. It did not not much argue for elderly people. In this study, SOC was able to obtain the suggestion that coping with an ordinary stress might contribute to capability with age.

PITX2 POSITIONS THE EMBRYONIC AXIS AND REGULATES TWINNING

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Embryonic polarity of invertebrates, amphibians and fish is specified largely by maternal determinants, which fixes cell fates early in development. In contrast, amniote embryos remain plastic, and can form multiple individuals until gastrulation. How is their polarity determined? The earliest known factor is Vg1 (GDF1), a TGFβ signal expressed posteriorly before gastrulation, acting together with Wnt. A molecular screen was performed in chick embryos to find upstream regulators of Vg1 in normal embryos and in embryos manipulated to form twins; this uncovers the transcription factor Pitx2 as a strong candidate. We show that Pitx2 is essential for axis formation, and that it acts as a direct regulator of Vg1 expression by binding to enhancers within neighbouring genes. Pitx2, Vg1 and Nodal are also key actors in left-right asymmetry, suggesting that the same, ancient polarity determination mechanism has been co-opted to different functions during evolution.

PSYCHOACTIVE MEDICATION IN A POPULATION-BASED TWIN SAMPLE: USE AND RELATIONSHIP WITH WELLBEING

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Introduction: Use of psychoactive medication is highly prevalent in the adult population. Psychotropic medication is usually prescribed by health personnel, but this is accompanied by high rates of self-medication. Consumption increases with age and it is higher in women than in men. It is important to analyze those factors underlying the use of psychoactive medication to be able to design better educational and health strategies. Our aim was to examine the relative contribution of environmental and genetic factors to the use of benzodiazepines (BZD) and its relationship with drug effect and wellbeing in a sample of adult female twins. *Materials and Methods:* Participants were 882 women from the Murcia Twin Registry (Spain) aged 57.11 years (*SD:* 7.28, range: 47–73). They were distributed in 181 MZ pairs, 168 DZ pairs, and 265 individual twins who were members of opposite-sex pairs. Data were obtained by telephone interview in the context of a broad study of general health conditions conducted in 2013. They were asked whether they had taken any kind of psychotropic medication in the last month, the name of the medication and the prescribed dose. The consumption of BZD (yes/no) in the last month was the selected phenotype. Tetrachoric correlations per zygosity group were calculated and a threshold model for categorical data was fitted to quantify genetic and environmental influences on variation in the prevalence of BZD consumption. Statistical analyses employed full information maximum-likelihood modelling procedures using the statistical package OpenMx. Zygosity was ascertained by questionnaire and DNA analysis. *Results:* BZDs were consumed by 23% of the women of our sample. One-third of them reported low or no relevant effect of the drug. Tetrachoric correlations were higher for MZ twins (rMZ = .48, (IC 95%: .21, .69) than for DZ twins (rDZ = .08, IC 95%: -.24, .39). suggesting the presence of genetic influences on the individual differences in BZD consumption. A univariate model was fitted to disentangle the sources of variance of this behavior. Since the DZ twin correlation was less than half the MZ twin correlation, D was estimated instead of C. Model fitting suggested that an AE model offers the best fit to data, A: .43 (IC 95%: .18,.65); E: .57 (IC 95% .35,.82). *Conclusion:* Preliminary results suggest that individual differences in use of BZD may be moderately but significantly influenced by genetic factors (h2 = .43). No evidence of shared environment has been found, being 60% of the variance explained by unique environmental factors and the measurement error. Genetic factors involved in this behavior may be related to the drug characteristics, or presence of psychopathology or specific personality traits. More research is needed to understand the factors underlying the use of psychoactive medication.

SOCIOECONOMIC STATUS AND SICK LEAVE GRANTED FOR MENTAL AND SOMATIC DISORDERS: A PROSPECTIVE STUDY OF YOUNG ADULT TWINS

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Introduction: Low socioeconomic status (SES) indicated by education and income has consistently been found to be a strong predictor of sick leave. This relationship is not simply explained by health differences. Several causal and non-causal explanations exist for the SES gradient in sick leave. This study utilizes a population-based sample of employed young adult twins to estimate the degree to which education and income are (1) prospectively related to the total level of sick leave and sick leave granted for mental and somatic disorders, and (2) whether these associations are confounded by familial factors. *Materials and Methods:* Registry data on educational attainment and income at age 30 and subsequent sick leave were available for 6,103 employed young adult twins. Population-level associations and fixed effects within twin pairs were estimated. *Results:* Low education and income were associated with sick leave granted for both mental and somatic disorders at the population level, and with the total level of sick leave. No associations between SES and sick leave were found within monozygotic twin pairs. *Conclusion:* Low SES indicated risk for sick leave granted for both mental and somatic disorders among young adults. Familial factors accounted for these associations. The observed associations were not consistent with low SES causing sick leave in young adulthood.

MECHANISMS OF ASSORTATIVE MATING FOR SMOKING BEHAVIOR IN A POPULATION-BASED TWIN STUDY

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Introduction: Spousal concordance for smoking behavior has been observed. The underlying mechanism remains largely unclear, but may be elucidated by analyzing data from twins and their spouses. The current study investigates the causes of assortative mating for current and lifetime smoking in a population-based sample of twins and their spouses. An additional sample of spouse pairs was formed by parents of twins. *Materials and Methods:* Smoking behavior was measured in surveys collected by the Netherlands Twin Register from 1991 up until 2011. Data were available for 28,077 adult participants, including 14,563 twins and 1,826 of their spouses (mean age 31.5 [*SD* 13.2]) and 11,688 parents of twins (mean age 55.4 [*SD* 8.2]). Assortative mating for smoking was examined by calculating correlations between twins and their spouses (rtw-sp), twins and their co-twin's spouses (rcotw-sp), spouses of both twins (rsp1-sp2) and parents of twins (rparents). With the unique twin-family sample we can distinguish the mechanism underlying assortative mating. Under phenotypic assortment, spouses directly select each other on their phenotype, resulting in the following pattern of correlations: rtw-sp > rcotw-sp > rsp1-sp2. If genetic influences are present, rcotw-sp and rsp1-sp2 will be higher in families of monozygotic (MZ) twins compared to families of dizygotic (DZ) twins. In case of social homogamy, spouses are more similar due to shared environment, resulting in equal correlations (rtw-sp = rcotw-sp = rsp1-sp2) and no MZ-DZ differences. Marital interaction hypothesizes that spouses become more similar over time. In that case, spouses of an older generation (rparents) will be more similar than those of a younger generation (rtw-sp). Additionally, a longer relationship will be associated with higher spousal similarity within each generation. *Results:* The first results show that for lifetime smoking, rtw-sp was 0.749 [95% CI = 0.705–0.788] while rparents was 0.268 [CI = 0.221–0.314]. For current smoking, these correlations were respectively 0.777 [CI = 0.728–0.819] and 0.511 [CI = 0.464–0.556]. For lifetime and current smoking, rcotw-sp was higher in MZ twins (resp. 0.579 [CI = 0.492–0.656] and 0.459 [CI = 0.338–0.569]) compared to DZ twins (resp. 0.277 [CI = 0.154-0.394] and 0.156 [CI = 0.003–0.304]). The same was true for rsp1-sp2 which was 0.864 [CI = 0.764-0.929] for lifetime and 0.778 [CI = 0.598–0.892] for current smoking in MZ-families and resp. 0.435 [CI = 0.184-0.642) and 0.088 [C I = -0.233–0.395] in DZ-families. Duration of relationship was not associated with higher spousal concordance. *Conclusion:* These results show significant spousal concordance for both lifetime and current smoking. The pattern of familial

correlations suggest phenotypic assortment as the main mechanism of assortative mating. Further analyses with structural equation models will determine which mechanism(s) is/are involved and what the consequences of assortative mating are for heritability estimates and genetic architecture of complex human traits.

CESAREAN DELIVERY FOR THE SECOND TWIN — AUDIT OF CLINICAL PRACTICE AT A LARGE TERTIARY REFERRAL CENTRE

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Introduction: Delivery of the second twin is one of the most challenging events for practicing obstetricians. Combined vaginal/cesarean delivery for twin pregnancies is associated with increased maternal and perinatal morbidity. For women who deliver the presenting twin vaginally, the risk of requiring a cesarean section (CS) for the second twin is 4%. Potential predictors of combined deliveries include: (1) vertex-nonvertex presentation, (2) gestational age (GA) >39 weeks at delivery, (3) discordance >25%, (4) twin-to-twin delivery interval >30 minutes, (5) after operative vaginal delivery of the presenting twin and (6) mothers with a history of subfertility. The aim of this audit was to establish the combined vaginal/CS delivery rate for twin pregnancies and to identify maternal, fetal and labor characteristics associated with this outcome. *Materials and Methods:* Medical records of women who underwent CS for the second twin between January 2009 and December 2012 were identified from the twin register at Cork University Maternity Hospital (CUMH), a large tertiary obstetric referral centre with over 8,500 deliveries per annum. A chart review was conducted identifying any maternal, fetal or labor characteristics associated with combined vaginal/CS delivery for twin pregnancies. *Results:* Between January 2009 and December 2012, 694 sets of twins were born at CUMH. The majority of these were dichorionic diamniotic twins (82%; $n = 568$); 44% ($n = 308$) had an elective CS delivery without labour. Of those who attempted a vaginal delivery ($n = 386$), 8 (2.1%) had a CS for the second twin following vaginal delivery of the presenting twin. All women in this audit were multiparous. Vertex–non-vertex presentation at delivery occurred in 75%($n = 6$) of cases. The delivery was abandoned when the presenting part did not enter the pelvis with maternal effort or where there was a malpresentation. Table 1 outlines maternal, fetal and labour characteristics. *Conclusion:* The risk of CS for delivery of a second twin was 2% in women who attempt a vaginal delivery for twins. This compares favorably with the national published data originating from the multicentre ESPRiT study. Skilled and safe delivery of a second twin demands the knowledge of obstetric maneuvers such as internal podalic version or external cephalic version. Preserving these skills is of great importance in clinical practice.

THE HERITABILITY OF EARLY MOTOR DEVELOPMENT IN 2-YEAR-OLD DUTCH TWIN PAIRS STRATIFIED BY GESTATIONAL AGE.

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Introduction: Motor milestones are recognizable landmarks of development in the first years of life. A delay in achieving motor milestones is often a first sign for further monitoring the development of a child. One of the risk factors for a delayed motor development is prematurity — especially very preterm birth is associated with impaired motor development (de Kieviet et al. 2009). The goal of this new study is to estimate the relative contribution of genetic and environmental factors on achievement of motor milestones and to test whether these factors contribute differently in term, preterm and very preterm born twins. *Materials and Methods:* The study is part of the longitudinal data collection of the Young-Netherlands Twin Registry on behavioral and emotional development. Data on motor development were available for about 21,500 twin pairs, born between 1987 and 2010, and obtained by maternal report. Weekly interviews on motor development were done in a subgroup. Motor development was assessed by the age of achieving a motor milestone (turning over, sitting up, crawling, standing, and walking). With structural equation modeling, we estimated the effects of genetic and environmental influences for term and preterm groups, separately. *Results:* A first exploration of the data revealed that prematurity is a significant predictor for attainment of motor milestones. As expected, preterm and very preterm born twins achieved the motor milestones later than term born twins. Across the 5 motor milestones, MZ twin correlations were around 0.90 and DZ correlations were around 0.70. *Conclusion:* This indicates both genetic and environmental influences. Across term and preterm groups, the pattern of MZ and DZ twin correlation was equal, suggesting that gestational age is not an explaining factor that contribute to the shared environmental variance.

MIDTERM CERVICAL LENGTH AS A RISK INDICATOR FOR CESAREAN DELIVERY IN TWIN PREGNANCY

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Introduction: In nulliparous women with a singleton pregnancy delivering at term, midterm cervical length (CL) is associated with the risk of emergency cesarean delivery.Women with a long cervix at mid-term had an increased risk of intrapartum cesarean delivery at term compared to those with a short cervix. Women with a singleton pregnancy and a short cervix are known to have an increased risk of (very) preterm delivery. In general, the shorter the cervix, the greater the likelihood that PTB will occur. The same holds for women with a multiple pregnancy. The association between CL and the risk of emergency cesarean delivery in women in labour with a multiple pregnancy has never been assessed. The aim of the present study is to identify whether midterm CL is a risk indicator of emergency cesarean delivery in multiple pregnancies. *Materials and Methods:* We used data from two multicenter randomised clinical trials conducted in the Netherlands (AMPHIA-study and ProTwin-study). All nulliparous women that started with a vaginal delivery after 34 weeks of gestation and had their first child in cephalic position were included in this analysis. We assessed the univariable association between risk indicators, including mid-term cervical length in quartiles, and emergency cesarean delivery using a logistic regression model. In multivariable analysis we assessed whether adjustment for other risk indicators altered the associations found in univariable (unadjusted) analysis. Separate analyses were performed for suspected fetal distress and failure to progress as indication for cesarean

section. *Results:* There were 311 women with a twin pregnancy who attempted vaginal delivery after 34 weeks of gestation. Emergency cesarean delivery was performed in 111 (36%) women, of which 67 (60%) were performed because of arrest of labour. There was no relation between mid-term cervical length and cesarean delivery (aOR 0.97; for CL p26-50, aOR 0.71 for CL p51-75 and aOR 0.93 for CL >p75 with CL ≤p25 as reference). In multivariable analysis, the only variables associated with emergency cesarean delivery were maternal age (OR 1.07; 95% CI 1-1.13) BMI (aOR 3.99 (95% CI 1.07-14.9 for BMI 19-23, aOR 5.04 (95% CI 1.34-19.03) for BMI 23-28 and aOR 3.1 (95% CI 0.65-14.78) for BMI > 28) and induction of labour (OR 1.9; 95% CI 1.05-3.5) (tabel). Separate analysis for indication of cesarean delivery showed that there was no relation between cervical length and failure to progress or suspected fetal distress as indication for cesarean delivery. *Conclusion:* In nulliparous women with a twin pregnancy, midterm cervical length is not associated with emergency cesarean delivery.

ASSESSMENT OF ORAL CONDITIONS IN TWINS

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Introduction: The study of twins provides a unique opportunity to evaluate the genetic and non-genetic contributions to a variance of multitude of traits. Twin research has revealed the impact of a strong genetic component to the variance of many dental traits. The present study was conducted in monozygotic (MZ) and dizygotic (DZ) twins to assess the quantity of saliva and salivary pH, oral hygiene status, dental caries, occlusion and dental arch measurements. *Materials and Methods:* A random sample of 129 MZ and DZ twin pairs aged 6–15 years from Bangalore were included in this study. The zygosity of the twins was initially recorded by facial appearance and later determined by dermatoglyphics. The assessment of oral conditions such as quantity of saliva, salivary pH, oral hygiene status, dental caries status, occlusion and dental arch measurements was performed in these twin pairs in the school in the presence of school authorities. The data was recorded and subjected to statistical analysis. *Results:* Moderate degree of agreement between zygosity determination by comparison of facial appearance and dermatoglyphics was found. The mean quantity of saliva, salivary pH, OHI-S scores, deft and DMFT, occlusal status and dental arch measurements were found to show no statistically significant difference in MZ twin pairs. The DZ twin pairs did not show any statistically significant difference in the oral parameters studied except for the mandibular arch length, which showed a moderate degree of significance. *Conclusion:* It was concluded from the present study that there were similarities in the dental traits observed in the MZ and DZ twin pairs with a chance variation in one of the parameters in DZ twin pairs, indicating a genetic influence on these traits. The determination of zygosity by dermatoglyphics seems to be a non-invasive and an acceptable method of determination of zygosity, as evidenced by this study.

QUALITATIVE ANALYSIS OF MONOCHORIONIC TTTS PARENTS DECISION-MAKING PROCESS

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Introduction: Women pregnant with multiples fetuses are at increased jeopardy for several high-risk conditions Twin-to-twin transfusion syndrome (TTTS) is a complex condition that threatens fetal life and wellbeing. TTTS is a medical condition diagnosed in multiple gestation pregnancies. The occurrence of TTTS is almost exclusively diagnosed in monochorionic (one placenta) pregnancies, which account for 20% of all twin gestations (Harkness & Crombleholme, 2005). Mortality rates reach 80–100% if the condition is undiagnosed and untreated (Harkness & Crombleholme). One of the treatment modes is Cord Coagulation, which is the sacrificing of one twin, therefore arresting the syndrome progression and prolonging gestation, thereby maximizing the outcome of the other twin (Harkness & Crombleholme). Patient participation in decision-making processes influences outcome, compliance and future quality of life implications. *Materials and Methods:* The aim of this study was to investigate the parents' decision-making process of the sacrificing of one twin. Qualitative interviews were undertaken with seven parents (in some cases solely mothers). The rationale for interviewing seven parents from wide span of cultural and religious backgrounds was to generate a rich multiplicity of viewpoints potentially spanning the domains of the decision-making theoretical structure by approximating patients' meanings and interpretations (Blaikie 2005, Polit & Beck 2008). *Results:* The main theme was that decision making was a journey, originating with the search for a competent, experienced physician who was knowledgeable in this procedure. Subthemes included information search, emotional support, living with the paradox of years of infertility and then sacrificing a fetus, and finally living with the consequences of the decision. Interesting to note was that the social context of all participants included a wide variety — from extreme religiosity to completely secular, from single mothers to heterosexual parents. *Conclusion:* The knowledge of the decision-making process assists health care providers in the ability to empower, understand and support their patients' profound difficulties, dilemmas, and heartbreak.

AMNIOCENTESIS IN DICHORIONIC TWIN PREGNANCIES DOES NOT INCREASE THE RISK OF ADVERSE OUTCOME UNTIL 24 WEEKS

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Introduction: The risk of fetal loss and preterm rupture of membranes (PROM) in twin pregnancies after amniocentesis is not clear and discordant results are referred. The aim was to compare the risk of fetal loss and PROM < 24 weeks between twin dichorionic pregnancies undergoing amniocentesis and a control group undergoing sonography at the same gestational age. *Materials and Methods:* We analyzed 327 dichorionic twin pregnancies referred to the Sant'Anna Hospital, Turin and to the Santa Croce Hospital, Cuneo (Italy) from January 2008 to October 2013. Among them we identified a study group of 163 women with twin pregnancies who had amniocentesis performed by experienced operators, and a control group of 164 women with twin pregnancies who had only an ultrasound scan performed at the same gestational age ($16 \pm 1{,}38$ weeks). Triplets, selective feticide, abnormal fetal karyotype and fetal malformations were not included in the study. *Results:* In both groups we observed an overall risk of fetal loss and PROM of 1.8%: in the study group we observed one case of spontaneous abortion before 20 weeks, one of spontaneous abortion between 20 and 24 weeks and one of PROM before 20 weeks of gestational age; in the control group we observed three cases of PROM before 20 weeks of gestational age. There was not a significantly increased risk of the complications considered in women who performed amniocentesis. *Conclusion:* In our study the incidence of adverse outcomes (fetal losses and PROM) until 24 weeks of gestational age in dichorionic twin pregnancies is not increased by amniocentesis.

URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN LEVELS IN TWIN PREGNANCIES COMPLICATED BY INTRAUTERINE GROWTH RESTRICTION

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Introduction: Twins pregnancies provide a unique opportunity to mimic a scientific experiment to study intrauterine growth restricted (IUGR) fetuses and, reflecting nutritional stresses within a similar genetic fetal background, to distinguish between genetic and environmental causes of phenotypic variations in human population. IUGR disorder may have adverse effects on the integrity and function of vascular endotelium during fetal life. NGAL (Neutrophil Gelatinous-Associated Lipocalin) is a glycoprotein expressed by neutrophils and various epithelial cells, with multiple functions, immune and transport. Its concentration increases in cases of inflammation, infection, heart disease and kidney disease. Whether IUGR twins present higher NGAL levels in utero is not known. *Materials and Methods:* Twin pregnancies were enrolled at 32 weeks gestation during routinary scan. In this analysis, IUGR twin fetuses were classified in 2 groups: Group A, if the estimated fetal weigh (EFW) was 2SD and Group B (Small for Gestational Age, SGA) if the EFW was <10th percentile, without velocimetry abnormalities. AGA fetuses were those with an EFW between the 10th and 90th centile. Amniotic albumin and albumin/creatinine ratio (ACR) and NGAL concentration were determined in an amniotic fluid sample, taken immediately before incision of membranes. *Results:* 394 twin fetuses were enrolled, of which 298 were classified as AGA fetuses, 61 fetuses as IUGR and 35 AGA. Median amniotic fluid albumin concentration (IUGR, Group A 1,42 g/L; IUGR, Group B 1,07 g/L; and AGA 1,24 g/L; $p = .01$) and median ACR were significantly higher in the group A IUGR twins, compared with the IUGR, group B, and AGA twin fetuses (Group A IUGR 183500 mg/g; Group B IUGR 64720 mg/g; and AGA 82750 mg/g; $p = .0002$). NGAL concentration was statistically different in the IUGR Group (169,3 ng/mL) to the AGA Group (158 ng/mL, $p < .05$), while in the SGA Group B (SGA) (128,4 ng/mL) and AGA were not found significant differences ($p = .28$). A negative correlation was also found between NGAL concentration and renal volumes in the IUGR group compared with the AGA group ($p = .05$). *Conclusion:* This natural model of pregnancy nutrient restriction showed that IUGR twin fetuses present higher albumin, ACR and NGAL levels in amniotic fluid, which could be possible markers in utero of early glomerulosclerosis.

THE FIRST QUINTUPLETS IN CZECH REPUBLIC

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Introduction: Short report about the first year of the first Czech quintuplets — their pregnancy, delivery, breastfeading, growth and progress, including the social aspect of the multiple birth from the position of Ministry of Labour and Social Affairs. Presentation of the facts of giving care to this family from the state, donors and NGOs and public. Part of the presentation is a short sample time-lapse documentary film about these first quintuplets. *Materials and Methods:* This is not research, but only a presentation of the first year of the quintuplets from the perspective of social work and health care. Material — short sample time-lapse documentary film. Method — presentation of the facts. *Results:* Exchange of good practice. *Conclusion:* Exchange of good practice.

NEUROLOGICAL AND COGNITIVE LONG-TERM DEVELOPMENT OF MONOCHORIONIC TWINS AFTER INTRAUTERINE LASER-THERAPY FOR TWIN-TWIN-TRANSFUSION SYNDROME

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Introduction: Twin-twin-transfusion syndrome (TTTS) occurs in approximately 10% of all monochorionic pregnancies, leading to a high perinatal mortality and morbidity if left untreated. Intrauterine laser-therapy is an effective, causal treatment option. In previous studies analyzing the neurologic long-term development after intrauterine laser surgery for TTTS, the age at examination was low, mostly 2 years. To define long-term neurological and cognitive development of twins after intrauterine laser-therapy for TTTS we performed examinations at a median age of 9 years and 10 months and compared the cognitive and neurological performance of these children with earlier examinations, which had been performed at the age of 2 and 6 years. *Materials and Methods:* In the study we examined 31 twin couples with a median age of 9 years and 10 months. They already had been examined with 2 and 6 years. We performed a standardised physical and neurological examination and three different intelligence tests: The Wechsler Intelligence Scale for children IV (WISC-IV), the Tower of London Test (TLT) and the Number connection test (NCT). The patients where grouped in three different outcome groups: Group I contained children with normal test results. Those in group II had minor neurological deficiencies. Children of group III had major neurological deficiencies like cerebral palsy or mental retardation with results of the WISC-IV below minus two standard deviations. *Results:* 52 children where in group I (83,9 %), 4 children belonged to group II (6,5 %) and 6 children to group III (9,7 %). Results of the WISC: IQ of the children ranged from 47 to 130 points. The median IQ was 92.5 points. Recipients ranged from 47 to 130 points, the median IQ was 93.5 points. Donors ranged from 52 to 129 points, with a median of 92 points. There was no difference between the IQ of donors and recipients with a p-value of 0.39. We also could not detect any differences in the WISC-subtests for donors and recipients. Results of the TLT: The TLT was performed with 60 children. The percent ranks of the whole group ranged from 4 to 99, the median was 73. The percent ranks of the recipients ranged from 4 to 99, the median was 73. The donors received 5 to 98 percent ranks, with a median of 74. The results of donors and recipients where equal with a p-value of 0.64. Results of the NCT: The IQ-points of the children ranged from 61 to 139, with a median of 109 for the whole group. The recipients achieved 64 to 139 IQ-points with a median of 112. The donors achieved 61 to 137 IQ-points with a median of 107. There was no difference between donors and recipients with a p-value of 0.38. *Conclusion:* Despite different prenatal pathophysiology of the twins, we did not find any differences in the cognitive development between donors and recipients.

HERITABILITY OF INTELLIGENCE THROUGH ADOLESCENCE: LONGITUDINAL STUDY

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Introduction: General intelligence (IQ) is a stable general cognitive ability which influences a broad range of human activities. Individual differences in IQ persist in any social group and population, and

can be explained by genetic and environmental factors. Heritability of IQ increases from childhood (40%) to adulthood (over 80%). In the present study we are trying to find out whether the same or different genetic and environmental factors determine individual differences in IQ at different ages through adolescence. *Materials and Methods:* We used the longitudinal data of Russian adolescent twins. IQ was measured by means of the Wechsler Intelligence Scale for Children-III (13-year-old twins) and Wechsler Adult Intelligence Scale-III (16-year-old twins). The sample was 215 twin pairs. We fit longitudinal twin models for Verbal IQ, Performance IQ, and General IQ scales. *Results:* IQ scales show high stability: 0.7–0.8. Verbal and General IQ are equally heritable: 30% of phenotypic variance is explained by genetic factors. Shared environment explains 50% of Verbal and General IQ variance. Performance IQ is more heritable (60%) and has higher impact of non-shared environmental factors (25%). All IQ scales entirely share genetic variance at 13 and 16, that is, there is no specific genetic variance at 16. The variance accounted for shared environmental factors at 16 is 30% specific for Verbal and General IQ and 50% specific for Performance IQ. Non-shared environmental variance at 16 is mostly specific for all IQ scales (90%). *Conclusion:* According to the results of our study, IQ develops under the influence of the same genetic factors through adolescence. Only half of shared environmental variance persists, and most of non-shared environmental variance is specific. This means that the stability of IQ is connected with genetic and common environmental factors (and possibly with gene-environment correlation or interaction) but not with individual environmental factors.

THE OUTCOMES OF TRIPLETS AND QUADRUPLETS BORN IN A SINGLE LEVEL III CENTRE OVER A 10-YEAR PERIOD

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Introduction: Multiple pregnancies are an increasing entity worldwide. This increase is attributed largely to artificial reproductive technology and fertility-inducing drugs. The percentage increase in triplet and higher-order births has been more dramatic than the increase in the percentage of twin deliveries. This is associated with an increase in the number of pregnancies complicated by preterm birth and intrauterine growth restriction, which in turn results in higher infant mortality rates. Additionally, an increased risk of cerebral palsy in multiples has been reported, being higher the higher the number of foetuses. *Materials and Methods:* The primary aim of our retrospective study was to determine two year outcomes of triplets and quadruplets born in the Coombe Women and Infants University hospital (CWIUH) over a ten year period and in particular the need for early intervention services. A retrospective chart review of all triplets and quadruplets born between January 2002 and December 2011 was performed. *Results:* There were 125 infants from triplet pregnancies and eight infants from quadruplet pregnancies live born in CWIUH during this period. One chart was unavailable for analysis. Therefore 132 infants were included in the study; 66 (50%) were conceived by in vitro fertilisation and 9 (7%) following clomiphene citrate treatment. All of the babies were delivered by cesarean section, 47 (36%) elective and 85 (64%) emergency; 77 (58%) were male and 55 (42%) female; 44 (33%) of the babies had intrauterine growth restriction (26 asymmetrical and 18 symmetrical). There was one case of twin-to-twin transfusion syndrome. One hundred and fifteen (87%) babies received complete antenatal steroids prior to delivery. Fourteen (11%) babies were born to mothers who had pre-eclampsia. Median gestational age was 33 + 2 (26 + 2 to 36 + 2) weeks. Median birth weight was 1800 (620 to 2960) g. Eighty two (62%) babies had respiratory distress syndrome. There were no cases of chronic lung disease. There were seven (5%) cases of intraventricular haemorrhage and two (2%) of periventricular leucomalacia. There were 17 (13%) cases of sepsis and 1 (1%) case of meningitis. The median length of stay in our neonatal unit was 23 (0 to 91) days. Two babies died at 2 months of age. Four (3%) were referred to early intervention services, one with spastic quadriplegia and three with mild left hemiplegia. Eleven (8%) were followed up by a community paediatrician following discharge from the neonatal clinic at two years of age. *Conclusion:* To our knowledge this is the first study to look at the outcomes of triplets and quadruplets in Ireland. Our outcomes are similar to those reported in the international literature which quotes an incidence of cerebral palsy in triplets of approximately 4%.

COMMON IMMUNE-RELATED EXPOSURES/CONDITIONS AND RISK OF NON-HODGKIN LYMPHOMA: A CASE-CONTROL STUDY IN DISCORDANT TWIN PAIRS

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Introduction: Common immune-related diseases or exposures, such as atopic disease or childhood infections, may affect the risk of non-Hodgkin lymphoma (NHL). Twins are an ideal population in which to study immune-related risk factors because they are partially or wholly matched on genome and family structure (both confounders), and they can recall differences in early life exposures having been compared all of their lives. We therefore conducted a matched case-control study of early life and immune-related exposures in twin pairs discordant for non-Hodgkin lymphoma. *Materials and Methods:* We evaluated common immune system-altering exposures in a case-control study of 162 like-sex twin pairs discordant for NHL, identified from the International Twin Study USC, Los Angeles, USA. Medical history and childhood behaviors associated with infection were ascertained from a mailed questionnaire. Conditional logistic regression was used to compute odds ratios and 95% confidence intervals. Questions were framed as direct with dichotomous (yes/no) responses and as intra-pair relative comparisons (who was exposed more?). Analyses were stratified by zygosity, respondent status (double or single respondent pairs), sex, and histological subtype. *Results:* 76 double-respondent and 124 single-respondent pairs returned completed questionnaires, a 72% response rate compared to a 60% rate among cases and 40% response rate among controls in a population-based study conducted during the same period. The majority (81%) of single-respondents were unaffected co-twins of deceased cases. Among double-respondent pairs agreement between twins on each other's exposure status was high (76%–97%). A strong inverse association between NHL and seasonal hay fever (OR = 0.28, 95%CI = 0.10–0.75) and certain specific allergies (OR = 0.29, 95%CI = 0.13–0.68) was observed. The number of atopic diseases was inversely associated with NHL (p trend = .0003). The inverse association between NHL risk and a number of these atopic conditions was stronger among DZ compared to MZ twins (any atopic disease: DZ twins OR = 0.12, 95% CI = 0,03, 0.51 vs. MZ

twins OR = 0.57, 95% CI = 0.24, 1.36). A history of infectious mononucleosis was also inversely associated with NHL risk (OR = 0.35, 95%CI = 0.14–0.90). There was no significant association with tonsillectomy or appendectomy. Behaviors associated with exposure to infection during early life were positively associated with NHL risk (p trend = .04). No differences in association by NHL subtype were observed, although statistical power for these comparisons was low. *Conclusion:* Our observations support the hypothesis that immune-related exposures, especially allergy, are associated with NHL risk. Using relative intra-pair comparisons in twins, we were able to ascertain exposure information about early life that would not otherwise be possible.

THE GENETICS BASIS OF COTININE LEVELS IN DAILY SMOKERS: RESULTS FROM A GENOME-WIDE META-ANALYSIS

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Introduction: Genome-wide association studies (GWAS) have facilitated the search for genetic factors that contribute to specific phenotypes. However, GWAS tend to employ relatively crude phenotypes (e.g., self-report measures), given the need to collect data on very large samples in order to have adequate power to detect the small effects of common variants on complex phenotypes. GWAS which use more precise phenotypes may have greater statistical power, and identify novel variants, compared to studies using less precise phenotypes. *Materials and Methods:* We conducted a GWAS of cotinine, the primary metabolite of nicotine, in a consortium of 11 samples (the Cotinine Consortium), comprising 4,588 daily smokers of European ancestry. Genotype imputation was performed using 1000 Genomes (Phase1 version3) as a reference panel. Results were combined in a meta-analysis. *Results:* Meta-analysis was completed for 11,011,721 variants. As expected, we observed association between multiple variants within the 15q25 region and cotinine level, all located within the CHRNA5-A3-B4 gene cluster or adjacent genes (minimum p = 1.46 × 10-19 for rs10851907). Conditioning on rs10851907 revealed evidence of a second independent signal in this region, marked by rs57064725 (pC = 2.92 × 10-8). We also observed an association with a novel locus on chromosome 4 within a region of UGT genes (minimum $p = 5.89 \times 10\text{-}10$ for rs114612145), which was consequently replicated in two independent samples. *Conclusion:* Our results at 15q25 correspond well with findings in previous much larger GWAS using self-report measures of smoking quantity. The association noted between cotinine and a novel locus at UGT2B10 on chromosome 4 may reflect a change in cotinine pharmacokinetics rather than an increase in tobacco exposure, although this requires further investigation. Our approach clearly illustrates the benefit of using precise, objective phenotypes in genetic association studies. However, the use of metabolite data (such as cotinine) as a proxy for environmental exposures should be carefully considered in the context of individual differences in metabolic pathways.

A CO-TWIN CONTROL STUDY OF THE RELATIONSHIP BETWEEN ANXIETY DISORDERS AND DIMENSIONAL REPRESENTATIONS OF DSM-IV PERSONALITY DISORDERS

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Introduction: A high rate of co-occurrence between anxiety disorders and personality disorders (PDs) has been reported in previous studies. To the authors' knowledge, the current study is the first one to explore these relationships within a co-twin control analytical framework. First, we aimed to investigate which PDs are associated with anxiety disorders in a population-based twin cohort. Secondly, we wanted to adjust the observed correlations for confounding latent genetic and non-genetic factors shared by the phenotypes. *Materials and Methods:* Young adult twins (n = 2,801), mean age 28.2 years, from the Norwegian Institute of Public Health Twin Panel were assessed by means of clinical interviews for lifetime DSM-IV anxiety disorders and the DSM-IV PDs. Using a confirmatory factor-analytic approach, one ordinal 'anxiety disorder'-variable comprising several diagnostic entities was constructed. For the PDs, ordinal variables based on a count of present diagnostic criteria were employed. 10 Poisson-regression analyses with 'anxiety disorder' as the dependent variable and each PD as an independent variable were performed before multivariate modeling including all PDs as regressors was executed. A similar analytic strategy was then employed within monozygotic (MZ) and dizygotic (DZ) twin pairs in co-twin control analyses, applying a random-effects approach to account for the inherent dependency in data sets including twins. All analyses were performed using the STATA 13 software package. *Results:* All 10 DSM-IV PDs were significantly associated with anxiety disorders in bivariate regression models. In the multivariate regression model, schizotypal, borderline, avoidant and obsessive-compulsive PD remained significantly and independently associated with anxiety disorders. The bivariate co-twin control analyses among MZ twin pairs revealed an increased risk of anxiety disorders in schizotypal, paranoid, borderline, antisocial, avoidant and dependent PD, while only borderline and avoidant PD predicted anxiety disorders in the multivariate model. *Conclusion:* The co-twin control analyses within both MZ and DZ pairs produced lower effect estimates compared to regression models without adjustment for potential unobserved confounders. This suggests that the observed pattern of co-occurrence among anxiety disorders and PDs can be largely accounted for by common liability factors, genetic and non-genetic, shared among these diagnostic constructs. In addition, the results from the multivariate co-twin control analyses may indicate that specific environmental risk factors for co-occurrence of anxiety disorders and borderline and avoidant PDs are not shared with other PDs exist. However, cautious interpretation is warranted, as the attempt to partial out the effects of such a wide range of possible confounding variables may have led to over-adjustment in the model.

INDIVIDUAL FEEDBACK ON PERSONAL RESEARCH RESULTS VIA THE NETHERLANDS TWIN REGISTER PORTAL: PARTICIPANTS LOVE IT!

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Introduction: All participants in the Netherlands Twin Register (NTR) receive a yearly newsletter and subgroups who participated in specific study protocols receive a study report. Still, participants often remark that they would like to receive more information, in particular individual feedback on the NTR questionnaires they complete every 2 to 3 years. Considering the financial and personnel strain of large-scale personalised feedback (>15.000 participants for any one survey), this was never an option. However, technological advances and a financial grant recently made it possible to develop an NTR Portal. *Materials and Methods:* The NTR portal allows participants after personal login to get an overview of the questionnaires they completed, to receive feedback on the various research projects their information was used for, and most importantly, to open their own personal reports. Personal reports include their own personal score on a topic, together with an explanation and NTR population averages. For instance, a participant can view his or her score on sensation seeking behavior and compare this to the average sensation seeking score for the own sex and age category. *Results:* More than 12,000 NTR participant have already received their portal login and within the first 2 weeks 15% of those accessed the data. Responses have been very positive, with participants sending thank you notes by email. As all participants who received a login had already completed NTR questionnaires, we will compare these access rate against the participation records and personality scores. *Conclusion:* In conclusion, large-scale personalised feedback is now possible and can help meet the growing demand of participants for feedback on their results, though care must be given to the nature of the feedback provided.

EXPLAINING INDIVIDUAL DIFFERENCES IN BMI: CONTRIBUTIONS FROM THE NETHERLANDS TWIN REGISTER

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Introduction: Over the past decades the prevalence of obesity has increased dramatically in westernised societies, strongly impacting the health care system as obesity is among others related to an increased risk of developing type II diabetes and cardiovascular disease. Twin and family studies have consistently shown that genetic factors explain most of the variation in body mass index (BMI) within the population, but considering the rapid increase in average BMI over the years, societal factors may still play a role. *Materials and Methods:* Within the Netherlands Twin Register, longitudinal data on BMI and related behaviors (e.g., exercise) in young twins, adult twins and their family members (N > 20,000) have been collected over a period of 25 years. In subsets of these individuals, DNA samples as well as data on cholesterol and glucose were also available. *Results:* Within adults, the application of a parent-offspring model confirmed high heritability for BMI (78%), while taking into account spousal resemblance in BMI (r = .22). In line with these results, discordance in BMI was not very prevalent within monozygotic twin pairs (3–17%), and was particularly low for long-term discordance (<3%). Discordant pairs showed differences in food intake, but not in exercise behavior. Data in young twins also showed no consistent association between leisure time exercise and BMI from childhood to young adulthood. When data on biomarkers was available, the twin with the high BMI showed a significant less favorable biomarker profile than the co-twin with low BMI, and though gene expression differences were not significant, the high ranking genes pointed to metabolic gene regulation and inflammatory pathways. *Conclusion:* Our studies thus confirm the dominant role that genes play in individual differences in BMI and suggest that the key to permanent weight loss lies in calorie restriction rather than increasing exercise.

ON THE ROLE OF NON-SHARED ENVIRONMENT FOR EXECUTIVE FUNCTIONING IN ADHD: A TWIN-DIFFERENCES DESIGN STUDY

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Introduction: The study of differences between monozygotic (MZ) twin pairs with respect to ADHD may provide novel leads to disentangle the environmental contribution driving its phenotypes. The aim of this study was to examine non-shared environmental influences on executive function in dimensionally defined ADHD. *Materials and Methods:* This study included 27 MZ twin pairs (7 female) aged 11–20 years being moderately to substantially discordant for ADHD traits as assessed by the Attention Problem (AP) scale of the Child Behavior Checklist/Adult Behavior Checklist. The twins completed the Wisconsin Card Sorting Test (WCST) for cognitive flexibility and Tower Test (TT) for foresighted planning. Two statistical approaches were used to analyze the data. First, correlations between ADHD trait intra-pair differences and WCST and TT scores were calculated. Second, the significance of those intra-pair differences on WCST and TT, using ADHD as categorical variable in clinically discordant pairs, was tested. *Results:* Both analyzing strategies revealed a link between ADHD on one hand, and foresighted planning and inhibitory control on the other hand mediated by non-shared environmental factors. The first statistical approach yielded positive correlations between intra-pairs differences on the AP scale and intra-pair differences on two subscales of the TT: Total Rule Violation (rs = .41) and Rule-Violation-Per-Item-Ratio (r = .38). Findings in categorically discordant pairs were consistent, showing within-pair differences on the same subtests (z = -1.63, p = .05, one-tailed and z = -1.60, p = .05, one-tailed). *Conclusion:* Findings confirm previous research suggesting ADHD

to be a quantitative extreme on a continuum with executive functions being a cognitive marker of ADHD traits. Non-shared environmental factors appear to influence planning skills and inhibitory control.

PROSOCIAL AND PRO-SELF BEHAVIOR BETWEEN TWINS: FINDINGS FROM THE DIFFERENTIAL PRODUCTIVITY TASK

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Introduction: Several theoretical viewpoints address the paradox of prosocial behavior: Kin selection theory (Hamilton, 1964a, 1964b) states that animals maximize their inclusive fitness by pursuing the reproductive success of their relatives. Alternatively, direct or indirect reciprocity is a key process conceptualized as leading to individuals helping each other (Trivers, 1971), as well as a focus on the relationships between individuals as an underlying mechanism for prosocial behavior (De Waal, 2008; Maner & Gailliot, 2007). In the present study, we address these non-exhaustive alternative explanations with regards to children's prosocial and pro-self behavior, with a large sample of twins who performed a task to obtain rewards for themselves or for their co-twin. *Materials and Methods:* The sample included 124 monozygotic and 273 dizygotic 6-year-old same-sex twin pairs, who are part of the Longitudinal Israeli Study of Twins (LIST). Differential Productivity Task: Children were asked to outline as many tree images during 1 minute under two conditions: pro-self, in which the number of trees outlined determined the prize that they would receive; and prosocial, in which each twin's prize is determined by the number of trees his/her co-twin outlined. Twin Relationship: We used the mother-reported Twin Relationship Questionnaire (Fortuna et al., 2010), which assesses four relationship dimensions: closeness, conflict, dependence, and rivalry. *Results:* A MANOVA revealed a significant difference between the two conditions, suggesting that the twins worked more efficiently for themselves than for their co-twins. An ANOVA revealed a significant gender effect, indicating that girls generally succeed more than boys in outlining trees, and a significant order by condition interaction was found. However, there was no evidence for a significant difference in performance between MZ and DZ twins in this task. The correlations between the twins revealed that in the pro-self condition, the correlation between MZ twins was significantly higher than the correlation between DZ twins. In contrast, in the prosocial condition, significant positive correlations were found in the performance of both MZ and DZ twins, with no significant difference between MZ and DZ twins, suggesting a degree of reciprocity unrelated to the genetic similarity between the twins. To understand the role of twins' relationships, we investigated the association between the four relationship dimensions and inter-twin prosocial behavior. Inter-twin conflict was negatively and significantly correlated with the prosocial score. *Conclusion:* Our results, demonstrating that MZ twins did not display more prosocial behavior toward each other as compared with DZ twins, along with the finding that in the prosocial condition the correlations in the performance of MZ and DZ twins did not significantly differ, indicate that at least under some conditions genetic relatedness does not determine prosocial behavior between twins. Our findings may be seen as incompatible with the kin selection theory, as was already found in different animal (Napper, 2013) and human studies (Burnstein, 1994; Stewart-Williams, 2007), and supports the notion that reciprocity in general, and reciprocal relationships (particularly low conflict), rather than genetic relatedness is more important for determining the twins' motivation for prosocial behavior.

MALTREATMENT AMONG SINGLETONS AND TWINS IN JAPAN: A POPULATION-BASED STUDY

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Introduction: To evaluate the degree of risk of maltreatment among singletons, twins, and triplets in Japan and identify factors associated with the increased risk using population-based data. *Materials and Methods:* In Japan, the Maternal and Child Health Law establishes that all infants should receive medical check-ups at <1 year, 1.5 years, and 3 years of age. Pediatricians perform the medical check-ups and public health nurses conduct a consultation on child rearing with the parents at that time. Consequently, these medical check-ups are given to almost 100% of children in Japan. Additionally, public health nurses and other healthcare providers support families that are concerned about maltreatment. The data from these medical check-ups and the records about maltreatment are filed in the city public health department. These data, except personal information, are then transferred into computerized files in A city. This city is a residential community and has a population of approximately 453,000 people. Birth numbers per year are approximately 4,700. The records of maltreatment are linked to the data regarding the medical check-ups. We analyzed the database of records of maltreatment and the medical check-ups for infants aged 1.5 years between April 2007 and March 2011. This database contained information regarding the type of maltreatment, perpetrators, gestation number, gestational age at birth, birth weight, maternal health condition, maternal job status, and cooperation from other family members or relatives in child rearing. The study was approved by the Ethics Committee of Osaka City University. *Results:* Between April 2007 and March 2011, 18,247 infants underwent medical check-ups in A city. Overall, 17,755 (97.30%) babies were singletons, 486 (2.66%) were twins, and 6 (0.03%) were triplets. There were 59 singletons and 8 twins who were documented to have experienced physical harm, emotional harm, and/or neglect. There was a significantly higher rate of twins who had substantiated maltreatment than singletons who had substantiated maltreatment ($p = .002$). Mothers were the alleged perpetrator in 75% of twins and 67.8% of singletons. There was a significantly higher rate of poor health in the mothers who were the alleged perpetrators than in those who were not were the alleged perpetrators ($p < .001$). *Conclusion:* There was a higher rate of twins who had experienced substantiated maltreatment than singletons who had experienced substantiated maltreatment. Additionally, it was indicated that mothers who were the alleged perpetrators tended to be in poor health.

MULTIPLE BIRTH AND MENTAL HEALTH FROM PREGNANCY TO 5 YEARS AFTER BIRTH: A PROSPECTIVE POPULATION-BASED COHORT STUDY

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Introduction: There is a lack of population-based studies on multiple births and maternal mental health. Having a high-risk pregnancy by bearing two or more children is a stressful life event. After the pregnancy awaits the stress of parenting several children, leading to

a high level of parental stress. The only previous cohort study on multiple birth and maternal mental health included a single measure of depressive symptoms at 9 months postpartum. To the best of our knowledge there are no previous cohort studies comprising several measurements of postnatal mental health across several years. Furthermore, previous studies have to a great extent focused on depression. There are no previous longitudinal cohort studies estimating the association between multiple birth and anxiety disorders. *Materials and Methods:* We used data from 94,499 pregnancies included into the Norwegian Mother and Child Cohort study. Information on plural birth was retrieved from the Norwegian Medical Birth Registry, and maternal mental health was assessed at the 17th and 30th week of gestation and 0.5, 1.5, 3, and 5 years postpartum. We predicted maternal mental health at each time point subsequently adjusted for (1) factors prior to fertilization (e.g., maternal age and in vitro fertilization); (2) factors during pregnancy; (3) factors at delivery; (4) child-related postnatal complications; and (5) depression or anxiety during pregnancy. *Results:* Adjusted for antecedents of plural birth, mothers expecting a plural birth had a normal risk for depression (RR = 1.02 [95%CI 0.89–1.16]) and anxiety (RR = 1.05 [95%CI 0.09–1.20]) at 17th week of gestation. However, plural birth was associated with maternal depression at 1.5, 3, and 5 years postpartum and maternal anxiety at 3 years postpartum. The trend was for the association to increase across time, and mothers of multiplets had a RR = 1.77 [95%CI 1.33–2.35] for depression at 5 years. Since mothers expecting plural birth had marginally better mental health during pregnancy, factors prior to fertilization increased the association with postnatal mental health. Child-related postnatal complications reduced the association between plural birth and postnatal mental health problems, but mothers of multiplets still had an adjusted RR for depression of 1.51 [95%CI 1.10–2.08]. *Conclusion:* Mothers expecting multiplets have better or normal mental health during pregnancy. After birth there is an increasing risk for depression up to 5 years of age. Our findings indicate that more is simply more, and mothers of multiplets have need for additional support several years postpartum.

SPOT THE DIFFERENCE AND KNOW THE SIMILARITY: GENETIC COUNSELING IN MONOZYGOTIC TWINS

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Introduction: The Netherlands Twin Register (NTR) was established in 1987 at the Vrije Universiteit for scientific research purposes and has resulted in numerous studies on heritability, gene x environment interactions, as well as gene finding studies. Recently, we started a collaboration between the NTR and the VUMC University medical center — a multidisciplinary outpatient clinic, TWIN-VUmc, focusing on medical issues related to twin status. Genetic counseling for twins is a key feature. In addition, we retrospectively analyzed consultations in adult and child twin counselees at our Department of Clinical Genetics, in order to determine how often their questions were related to their twinning status and whether being a twin influenced or should have influenced the counseling. *Materials and Methods:* The twin status of every person visiting our (outpatient) clinic should be registered; until 2012 this registration was incomplete, but in the majority of counsels their twinning status was registered. We retrospectively analyzed over 500 consultations in adult and child twin counsels, who visited our outpatient clinic or were admitted at our hospital from 1990–2013 and were seen for genetic counseling. For all cases, we evaluated whether the reason for referral, outcome of genetic tests and genetic counseling aspects, such as the decision to perform genetic tests, the sibling or offspring recurrence risk, or outcome of genetic counseling was influenced by the twinning status. We evaluated the genetic counselings performed since the start of TWIN-VUmc. *Results:* From our first experiences and evaluation, it is obvious that being a twin or multiple influences genetic counseling in many aspects. In particular, with genetic counseling in monozygotic (MZ) twins, complex issues can be faced in risk estimation and counseling. Both Mendelian and more complex inheritance should be taken into account. In addition to the common approach, zygosity, concordance rates, heritability estimates and the occurrence of specific phenotypes in twins should be included in the analysis. In rare cases, MZ twins can be discordant at the DNA sequence level or epigenome, causing a discordant phenotype. Moreover, a concordant phenotype in MZ twins indicates a (strong) genetic contribution and increases the likelihood of a (mono)genetic cause. Many questions regarding inheritance raised by (MZ) twins are related to their twinning status to some extent. Also, twins often have questions about the heritability of twinning and zygosity. Importantly, in MZ twins, there is often a need to make a joint decision whether to test or not, because the test results of one twin are also informative for the co-twin. We will illustrate these unique aspects of genetic counseling in twins with our experiences at TWIN-VUmc (www.twinvumc.nl). *Conclusion:* Genetic counseling in twins requires insight in unique aspects of twin biology. Whereas in dizygotic twins or singleton siblings genetic counseling is mainly based on (strong) Mendelian genetic factors, in monozygotic twins total heritability should be taken into account. As such,