1.2 NOVEL APPROACHES TO UNDERSTANDING RISK

Chair: Prof. Gary Macfarlane, UK

01-2.1 THE USE OF REMOTE METHODS IN THE CONDUCT OF GENE-ENVIRONMENT INTERACTION STUDIES

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Background The scientific value of large-scale prospective gene-environment interaction (GxE) studies is widely accepted. However, these studies are prohibitively expensive and few are conducted. This approach, therefore, remains under-exploited. The ability to conduct prospective GxE studies entirely remotely, that is, without direct participant contact, promises substantial cost savings and would increase our capacity to utilise this design.
Aim To investigate the feasibility of conducting GxE studies entirely remotely by recruiting older people to a pilot study of cognitive function and subjective well-being.
Methods A random sample of men and women aged 50+ years and living in Cardiff, South Wales were mailed inviting them to visit a website to join a study of successful ageing. Online consent was obtained for questionnaire completion, cognitive testing, re-contact, record linkage and genotyping. Cognitive testing was conducted using the Cardiff Cognitive Battery. Bio-sampling was randomised to blood spot, buccal cell or no request.
Results A heterogeneous sample of 667 men and women (50% female) aged 50–101 years (median=62 yrs) from diverse backgrounds (representing the full range of deprivation scores) was recruited. Bio-samples were donated by 70% of those agreeing to do so. Self-report questionnaires and cognitive tests showed comparable distributions to those collected using face-to-face methods.
Conclusion This study has demonstrated that remote methods can be used to recruit for GxE studies and provides encouragement that up-scaling these methods provides the means to conduct large-scale GxE studies cost-effectively.

01-2.2 SPARSE INSTRUMENTAL VARIABLES: AN INTEGRATIVE APPROACH TO BIOMARKER VALIDATION

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We introduce the Sparse Instrumental Variable (SPIV) framework for distinguishing causal and non-causal explanations of associations between biomarkers and diseases. SPIV overcomes the key limitations of the classic instrumental variable (Mendelian Randomisation) methods for learning the direction of causality, by allowing for pleiotropic genotypic effects on disease outcomes. SPIV extends the recently introduced Likelihood-based Causality Model Selection approaches by jointly modelling the effects of multiple instruments and biomarkers in the presence of latent confounders and measurement noise. Where the biomarkers are gene expressions, SPIV can be used for fine mapping of quantitative trait loci detected in genetic linkage studies.

Our framework relies on sparse Bayesian linear modelling, which offers a rigorous approach to model comparison, and is particularly useful for addressing p>>n problems of genetic epidemiology. SPIV is inspired by automatic relevance determination and adaptive shrinkage methods, but is used for causal discovery and quantitative trait loci fine mapping rather than regression.

We demonstrate our framework by examining effects of gene transcript levels in the lung and liver on 40 quantitative traits in a sample of 260 mice from a heterogeneous stock. The full set of biomarkers consisted of over 47 500 transcripts and 100 000 genotypic instruments. We identify genes predictive of the considered traits, and show evidence of a direct causal relationship between Smurf2 and the CD4/CD8 ratio. We show that our approach has wide application in identification of biomarkers as possible targets for intervention, or as proxy endpoints for early-stage clinical trials.

01-2.3 A FAMILY-BASED STUDY OF THE NATURE OF SOCIOECONOMIC INEQUALITY IN PRETERM BIRTH AND SMALL FOR GESTATIONAL AGE IN DENMARK AROUND THE TURN OF THE MILLENNIUM

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Introduction A large body of literature has reported associations between socioeconomic position (SEP) and adverse pregnancy outcomes even in affluent egalitarian welfare states. It is unclear if this is interpretable as a causal effect of SEP. This study seeks to explore the nature of this relationship by examining women who change SEP between pregnancies and women who are siblings but are different in terms of SEP.
Methods Data consist of 471 215 live born singletons born in Denmark 1997–2007, who has at least one sibling or one first cousin. We examined maternal educational attainment and household income in relation to preterm birth and small for gestational age using Cox regression.
Results Household income was not related to the outcomes in cohort analyses, within mothers who were siblings or children who were siblings. Maternal education was associated with preterm birth only in the cohort analyses, where the least educated women had the highest risk. This suggests that factors that originate in the mother's early life, for example, shared genes or early life environment, explain the association. Maternal education was inversely associated with small for gestational age in cohort analyses and within mothers who were siblings, but not between children who are siblings. This suggests that the association was explained by factors that were persistent over the mother's pregnancies, but not shared between the mother's siblings.
Conclusion The association between maternal education and the outcomes cannot be interpreted as a causal effect. The association is likely caused by factors established in childhood or young adulthood.

01-2.4 HYPERTENSIVE DISORDERS OF PREGNANCY AND OFFSPRING VASCULAR, INFLAMMATORY AND LIPID OUTCOMES IN CHILDHOOD: FINDINGS FROM THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN

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Introduction Offspring of hypertensive pregnancies have higher blood pressure (BP) in later life. Whether this is accompanied by impaired vascular function and worse cardiovascular risk profiles suggesting mediation by intrauterine exposure to vascular toxins and long term programming, or is restricted to hypertension consistent with a genetic predisposition, is unknown. Specificity of association would be a useful test of these alternatives.

Methods We examined the associations of maternal gestational hypertension and preeclampsia with offspring vascular outcomes (endothelial dysfunction assessed by radial artery flow-mediated dilatation, arterial stiffness assessed by carotid to radial pulse wave velocity, brachial artery distensibility and BP) and with markers of inflammation (C reactive protein and Interluekin-6), lipids (triglycerides, high density lipoprotein cholesterol, non-HDLc) and apolipoproteins A1 and B assessed at age 9–12 years in a UK cohort (N=3127–4624).
Results We confirmed previous associations of both preeclampsia and gestational hypertension with offspring systolic BP (confounder adjusted mean differences: 2.37 mm Hg (95% CI 1.66 to 3.08) and 2.17 mm Hg (95% CI 0.39 to 3.95) comparing offspring of women with gestational hypertension and preeclampsia, respectively, with normotensive women) and diastolic BP (1.31 mm Hg (95% CI 0.69 to 1.92) and 1.40 mm Hg (95% CI −0.14 to 2.95)). However, we found no associations of either preeclampsia or gestational hypertension with endothelial dysfunction, any of the other vascular outcomes, inflammatory markers, lipids or apolipoproteins.
Conclusion The specific association of both preeclampsia and gestational hypertension with higher BP in offspring supports the underlying mechanism being due to genetic variants related to higher BP, rather than intrauterine mechanisms related to inflammation and endothelial dysfunction.

01-2.5 FALLIBILITY IN ESTIMATING INDIRECT EFFECTS: MISCLASSIFICATION OF THE MEDIATOR MATTERS MORE THAN COLLIDER BIAS

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Introduction Smoking is the largest single cause of preventable mortality and morbidity in Australia and many countries globally. The limited existing evidence suggests that smokers user fewer general practitioner (GP) services, but more hospital services, than non-smokers, and may not be benefitting from secondary prevention. We investigated use of GP services by Australians aged 45 years and over according to smoking status.
Methods Analysis of self-reported questionnaire data from 96, 522 participants in a population-based cohort study (the 45 and up Study), linked with data for national health insurance (Medicare) benefit payments and out-of-pocket-costs (OOPC). Generalised linear models were used to explore the relationships between smoking status, benefits paid and OOPC incurred. RRs were adjusted for age, sex, rurality, income, education, bodyweight, self-rated health, functional status and chronic conditions.
Results Current smokers were much less likely than non-smokers to be in the top cost decile for either benefits (RR 0.76, 95% CI 0.69 to 0.84) or OOPC (RR 0.61, 95% CI 0.55 to 0.68). Smokers used fewer preventive GP services (health checks, screening).
Conclusion Data linkage allowed complete capture of GP service use for a large population-based sample. After adjusting for a wide variety of access- and need-related factors, we found that Australian smokers are less likely than non-smokers to incur high costs for GP services. This held both for services provided for free, and those paid for by patients. Smokers may seek care less actively, perhaps because they are less health-conscious, or perhaps because they are avoiding censure from health professionals.

01-2.6 INTERGENERATIONAL CONTINUITY OF GESTATIONAL DURATION IN THREE GENERATIONS OF SWEDISH MALES AND FEMALES

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Objective We analysed associations between gestational duration in grandchildren and their biological grandparents.
Methods The Uppsala Birth Cohort Multigenerational Study includes manually collected archive data on a representative cohort of males and females born in Uppsala, Sweden 1915–1929 and information on descendants of the cohort obtained through linkage to routine data registers. Using path analysis, we analysed 7915 grandparents and their 26 423 grandchildren, where the grandparent, the grandchild and the intermediate biological relation were singletons. Maternal grandmothers, maternal grandfathers, paternal grandmothers and paternal grandfathers were considered separately. Models were adjusted for social variables and fitted separately for male and female grandchildren due to evidence of effect modification by sex.
Results Gestational duration in grandparents was positively associated with gestational duration in their grandchildren. The observed direct effects are equivalent to a 0.3–0.4 ($0.01 \leq p \leq 0.07$) day increase in the grandchild's gestational duration for each additional week in the maternal grandparents' gestational duration and 0.1–0.2 ($p \geq 0.2$ in all models) day increase in the grandchild's gestational duration for each additional week in the paternal grandparents' gestational duration. Distinct and gender specific patterns of statistically significant associations were observed for risk of preterm and post-term birth across generations. Birthweight-for-gestational age in maternal grandfathers was positively associated with gestational duration in their grandchildren while birthweight-for-gestational age in paternal grandfathers was inversely related to gestational duration in their grandsons.
Conclusion Gestational duration in maternal grandparents is positively associated with gestational duration in their grandchildren. Birthweight-for-gestational age in paternal grandfathers influences gestational duration in their grandchildren negatively.