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.