School of Social & Community Medicine

PhD Topics on Epidemiology, Public Health, Primary Care and Health Services Research 2014

SUMMARY OF TOPICS

	Supervisor	Title of project
1	Jonathan Evans and Rebecca Pearson	The impact of perinatal depression on maternal responsiveness, offspring development and psychopathology, exploring alternative mechanisms and differential susceptibility hypotheses.
2	Matthew Hickman & Rona Campbell	Quantitative and qualitative assessment of injecting risk and drug using networks: developing better behavioural surveillance and effective transmission models of BBV transmission among IDU
3	Matthew Ridd	Eczema Treatment in Children (ETC).
4	John Henderson & Jonathan Sterne	The origins of chronic obstructive pulmonary disease (COPD) in childhood
5	Esther Crawley	Improving access to specialist CFS services by ethnic minorities and other disadvantaged groups
6	John Macleod	Causal inference in observational studies of substance use
7	Matthew Hickman	Modelling the transmission of Hepatitis C and HIV, and the impact of prevention strategies among injecting drug users in UK
8	Katarzyna Kordas& Yoav Ben-Shlomo	Early exposure to environmental toxicants and parent-child relationship
9	Ruth Kipping & Russ Jago	Child obesity and the role of childcare settings: identifying risk factors and barriers/facilitators to reduce risks
10	William Hollingworth &Amanda Owen-Smith	The decline and fall of obsolete medical technologies

11	John Henderson & Raquel Granell	Air pollution and respiratory health in childhood
12	Jane Blazeby & Sara Brookes	Making Patient Reported Outcomes (PROs) from randomised controlled trials (RCTs) interpretable for clinicians to use in decision-making in surgical oncology
13	Kate Tilling, Laura Howe, Abi Fraser, Corrie Macdonald-Wallis, Debbie Lawlor	Diurnal patterns of physical activity, sedentary behaviour, heart rate and blood pressure in adolescents
14	Cathy Williams & Iain Gilchrist	The Cognitive Neuroscience of Developmental Simultagnosia
15	Bruna Galobardes	Early life inequalities in asthma: estimating its burden and understanding its aetiology
16	John Potokar & Rob Andrews	Stress responses in obesity
17	Richard Huxtable	Legal, Ethical and Clinical Dilemmas at the End of Life
18	Carol Joinson & Jon Heron	Risk factors for depression in adolescence
19	Carol Joinson & Jon Heron	Early Temperament and Vulnerability to Depression in Adolescence: The Role of Parenting and Parental Characteristics
20	Kate Northstone & Jon Tobias	Different methods of dietary patterns and their associations with bone development in childhood and adolescence
21	Julia Wade & Jenny Donovan	Optimising informed consent processes during recruitment to Randomised Controlled Trials (RCTs): a mixed methods investigation.
22	George Davey Smith, Sarah Meddows, Marcus Munafo	Digit ratio, development, gender orientation and disease

23	Alastair Hay & Pete Blair	What is the effectiveness of ‘real world’ delayed antibiotic prescribing and can “ScriptSwitch” increase its use?
24	Jon Heron and Matt Hickman	Influence of adolescent alcohol misuse on antisocial behaviour and depressive symptoms in young adulthood.
25	Richard Martin, George Davey-Smith , Caroline Relton	Epigenetic biomarkers of prostate cancer risk
26	George Davey Smith, Laura Howe, Thorkild I Sørensen , Jennifer L Baker	Epigenetic and metabolomic mediators of associations between childhood growth and chronic disease
27	Alastair Hay & Patricia Lucas	Can we determine the appropriateness of primary care consultations for children with RTI?
28	Bruna Galobardes	Life course area deprivation and the risk of asthma and atopy phenotypes in childhood and early adolescence.
29	Abigail Fraser, Corrie Macdonald-Wallis, Kate Tilling	Maternal haemoglobin in pregnancy: trajectories, risk factors and consequences for offspring. The Avon Longitudinal Study of Parents and Children (ALSPAC)
30	Abigail Fraser, Laura Howe, Gene Feder	Childhood abuse and intimate partner violence and their long term health sequelae: the Avon Longitudinal Study of Parents and Children
31	Laura Howe, Abigail Fraser	Age at puberty and cardiometabolic health in adolescence
32	John Macleod and Katy Turner	How strong is the evidence that interventions intended to reduce unplanned conception in adolescent girls have influenced recent rates in teenage pregnancy in England: review of reviews and analysis of routine data
33	Kerry Avery, Jane M Blazeby & Paula Williamson	Improving the design of pilot work to inform main RCTs in surgery

34	Nicky J Welton, Sofia Dias & AE Ades	Powering trials on effectiveness and efficacy outcomes
35	Shelley Potter, Jenny Donovan & Jane Blazeby	Optimising the design and conduct of screening logs within pragmatic trials to understand and improve recruitment
36	Nicky J Welton, Sofia Dias & AE Ades	Synthesis and Value of Information for trial design with surrogate outcomes
37	Alastair Hay and Pete Blair	Do antibiotics reduce risk of complications in children with respiratory tract infections?
38	Peter Vickerman, Matthew Hickman and Natasha Martin	Mathematical modeling of the impact of HCV vaccination among people who inject drugs
39	Peter Vickerman, Matthew Hickman and Natasha Martin	Mathematical modeling of an emerging epidemic: sexual hepatitis C transmission among HIV positive men who have sex with men
40	Judi Kidger	Factors Affecting Secondary School Staff's Mental Health
41	Hayley Jones, Matthew Hickman and Barbara Kasprzyk-Hordern	Waste water epidemiology – how can waste water analysis be incorporated or replace other epidemiological measures of substance use
42	Sarah Lewis and Caroline Relton	An investigation of intra-uterine nutrition and prenatal development– applying the principle of Mendelian randomization

Title: The impact of perinatal depression on maternal responsiveness, offspring development and psychopathology, exploring alternative mechanisms and differential susceptibility hypotheses.

Description:

Examining the impact of perinatal depression and maternal responsiveness on offspring development and psychopathology, exploring alternative mechanisms and differential susceptibility hypotheses.

This will include investigating the association between perinatal depression and mother's processing of infant stimuli as well as exploring the impact of perinatal depression on later child and adolescent psychopathology in the ALSPAC cohort, exploring alternative mediating mechanisms.

References:

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal depression and child psychopathology: a meta-analytic review. Clin Child Fam.Psychol.Rev., 14, 1-27.
Pearson, R. M., Cooper, R. M., Penton-Voak, I. S., Lightman, S. L., & Evans, J. (2010). Depressive symptoms in early pregnancy disrupt attentional processing of infant emotion. Psychol.Med., 40, 621-631.

Supervisors:
Jonathan Evans and Rebecca Pearson.

Title: Quantitative and qualitative assessment of injecting risk and drug using networks: developing better behavioural surveillance and effective transmission models of BBV transmission among IDU

Outline of Project:

Background:

The main thesis is that current measures of injecting risk behaviour are not informative – and if taken at face value may be misleading - and that better measures may be (and must be) obtained through new qualitative and quantitative assessment. Injecting risk behaviour, principally through sharing of used syringes, is a key factor determining the transmission and spread of HCV, HIV and HBV (i.e. blood borne viruses, BBV) among injecting drug users (IDU) [HPA Shooting Up]. Over 80% of diagnosed HCV infection, ~40% of HBV reports, and ~5% of HIV infection is attributed to IDU. The latest evidence also suggests that current or ex-IDU contribute ¾ of the estimated 200,000 HCV cases in England and Wales.

However, current surveillance and research data suggest that HCV incidence recently increased, and since 2001 there has been an ongoing increase in HCV prevalence [Judd 2005a, Sutton, HPA]. Moreover HIV prevalence, after remaining stable at low endemic levels for a decade, is now rising, and there have been marked increases in reports of injecting related bacterial infections [Hope, HPA]. HPA UAPMP data on sharing reported an increase in 1997, but no changes since then, but the analytic value and interpretation of these data is limited [Hope personal communication]. There are 3-fold differences in HCV prevalence among IDU in different geographical settings, for example, from ~20% in rural South Wales and North East England to 60% in London, Manchester and Bristol [Hickman et al, NPHS Wales in prep]. Furthermore recent data from a large study in Wales suggests considerable variation in HCV incidence on a smaller town/city level. Current data on sharing from UAPMP, longitudinal, or enhanced surveillance studies do not predict HCV/BBV infection, and fail to explain the geographical differences in HCV prevalence [e.g. Judd 2005b]. The evidence points to increased risk of HCV infection among homeless and crack IDU, and very recently to substitution treatment as potentially protective.

We believe all three of these factors are mediated through changes in injecting risk i.e. increasing or reducing injecting frequency, size and rate of change of drug sharing group, and syringe sharing events. However, these proximal measures of injecting risk may not be measured with the same degree of accuracy or reliability i.e they are misclassified. Moreover, we believe there maybe a parallel with explaining geographical differences in STI prevalence – where the degree of concurrency between partners rather than average number of sexual partners was the key predictor [Morris]. In contrast, some epidemiological studies emphasise associations between HCV and sharing paraphernalia [Mathei] – suggesting that public health messages also should target paraphernalia as a key transmission risk. Though self-reported behaviours among IDU have been validated [Darke], the research did not extend to sharing, which has been shown to be influenced by social desirability and under-reported in certain study conditions [Crane personal communication]. Initial work on developing a dynamic HCV transmission model for London and UK highlighted key uncertainties in both biological (e.g. viral clearance) and behavioural parameters (sharing frequency), which if one or other was resolved would substantially improve the model projections [Vickerman].

Objectives and Design: The thesis will be explored in three linked parts.
First, the study will test the hypothesis that current measures of injecting risk are not informative. Current systematic reviews of HCV, HIV and HBV prevalence and associations with sharing and injecting risk will be updated. Analyses of UK surveillance data, and other EU data in partnership with EMCDDA, will be conducted to test the strength of association between sharing and HCV infection and whether differences in reported sharing behaviour can explain differences in HCV prevalence. A review of the qualitative literature on reporting problem behaviours also will be conducted to assess reasons for under-reporting socially undesirable behaviours, and what recommendations have been made to reduce under-reporting.

Second, (and the main part) the study will test the hypothesis that more accurate and better measures of injecting risk can be obtained. A range of qualitative and quantitative surveys of IDU in two settings will be conducted: Bristol and Newport one high and one low HCV prevalence area. This part of the study will allow training in respondent driven sampling (RDS) methods for recruiting IDU. The surveys will explore a series of questions, which will be extended and refined by the qualitative surveys and potential data demands of HCV transmission model. For instance:-

- does self-completion of sharing behaviour under-report sharing frequency
- can qualitative assessments increase reported sharing
- are there reliable proxies for sharing injecting equipment
- what techniques may solicit more accurate responses (e.g. CASI, anonymised response, scenarios)
- what is the ratio of sharing paraphernalia: sharing injecting equipment
- is homelessness associated with greater size and rate of change in drug sharing partners
- what other factors are associated with size and rate of change of sharing partners
- what is the level of concurrency in drug and syringe sharing, and can it predict HCV infection
- what do users recommend for measuring injecting risk
- can users assess lifetime injecting risk
- to want extent does the identity of the interviewer/researcher influence responses

Third, the study will consider whether behavioural surveillance of injecting risk can be improved. It will evaluate the information in relation to CDC and HPA guidelines on evaluating surveillance programmes. In addition, this part of the study will consider:- whether sero-surveillance data are sufficient to inform public health action; whether better information can be obtained for informing and reducing uncertainty within transmission dynamic models; and the utility and recommendations of changing ongoing surveillance.

Milestones: The three parts correspond to the three years of the PhD. The first year will be used to conduct literature review, receive analytic training and analyse surveillance data, and set up fieldwork for second year. Second part and fieldwork will be conducted in 2nd year. Third part and final write up will be conducted in last year.

References:
Darke S. Self-report among injecting drug users : a review. Drug and Alc Dependence 1998; 51: 253-63
Hickman M, Hope V, Brady T et al. Hepatitis C (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004. AJE submitted
HPA Shooting Up: infections in injecting drug users in the United Kingdom, 2002. (V Hope et al.). Eurosurveillance; 8 (4) 22 January 2004

Hope VD, Judd A, Hickman M, Sutton A, Stimson GV, Parry JV, Gill ON. HIV prevalence among Injecting Drug Users in England & Wales 1990 to 2002: Evidence for increased transmission in recent years. AIDS 2005; 19: 1207-14
Judd A, Hickman M, Jones S, McDonald T, Parry JV, Stimson GV. Incidence of hepatitis C virus and HIV among new injecting drug users in London – prospective cohort study. BMJ 2005; 300: 24-25 (a)
Judd A, Hutchinson S, Wadd S, Hickman M et al. Prevalence of, and risk factors for, hepatitis C virus infection among recent initiates to injecting in London and Glasgow. Journal of Viral Hepatitis 2005; 12: 655-62 (b)
Mathei et al. Evidence or a substantial role of sharing of injecting paraphernalia other than syringes /needles to the spread of HCV among IDU. J Viral Hepatitis 2006; doi:10.111/j.1365-2893.2006.00725.x
*Morris M, Kretzschmar M. Concurrent partnerships and the spread of HIV. AIDS 1997, **11**:641-648.*
Sutton AJ, Gay NJ, Hope VD, Hickman M. Modelling the Force of Infection for Hepatitis B, Hepatitis C, and HIV in Injecting Drug Users in England and Wales. BMC infectious diseases (in press)
Vickerman P., Hickman M., Judd A. Modelling the impact of hepatitis C transmission of reducing syringe sharing: London case study. International Journal of Epidemiology (in press)

Research supervision:
Dr Matthew Hickman, Professor Rona Campbell

Title: Eczema Treatment in Children (ETC)

Proposal:
Atopic eczema (AE) affects ~20% of children and most are managed in primary care. However, we know little about the diagnosis or treatment of childhood AE by general practitioners (GPs). Only a handful of studies have examined the severity of AE in the community, none of which used objective or patient-reported measures. Information on how often children with AE see a GP is similarly sparse. The figure reported by Simpson et al of ~4 consultations per year includes adults as well as children and visits not related to eczema. Available primary care prescribing data in the United Kingdom (UK) are not linked to specific conditions. Allowing for this limitation, it would appear that GPs under-prescribe emollients and over-use topical corticosteroids (Santer *et al* 2006). Carers may commonly use complementary or alternative medicines (CAM) or apply significant dietary restrictions, yet GP awareness of or involvement in these decisions is unknown. Possibly four-fifths of the children referred to secondary care (mild or moderate disease severity) could be managed in primary care. Therefore work is required to establish how often children with AE attend their GP (and why), how severe the eczema is from the perspective of both carer and doctor, what treatments are prescribed by doctors and used by carers, and what prompts GP referral to a dermatologist.

Outline of Project

Aim: To examine the needs and treatment of children with AE in primary and secondary care.

Objectives: 1) To examine the pattern of contacts that children with AE have with primary and secondary care; 2) To compare the severity of childhood AE and treatments prescribed in primary and secondary care; 3) To identify factors associated with referral from primary to secondary care; 4) To compare clinician and carer assessment of AE severity; 5) To examine carer use, and GP awareness, of CAM and dietary exclusions; 6) To explore GP knowledge and confidence in the diagnosis, management and referral of children with AE.
Data collection and analysis: 30 practices in and around Bristol will be recruited to support a three phase, mixed methods study. Phase 1 Carer and GP survey and medical record review. Carer questionnaire (of children aged 12 years or younger with a diagnosis of AE) will comprise: Patient-Oriented Eczema Measure (POEM), impact of the condition on child and family, and use of prescribed and alternative medicines, and any dietary allergies/exclusions. GP questionnaire: management of children with eczema in general; regarding participants, eczema severity rating (physical severity and quality of life/psychosocial impact), and knowledge of treatments (including alternative medicine use and food allergies/restrictions). With permission, information on clinic and telephone contacts (including reason for the encounter) and treatments prescribed will be extracted from children's primary (and where relevant secondary) care medical records. Phase 2 A sub-sample of patients will be invited, by random selection stratified on the basis of carer-reported severity, to undergo an objective assessment of eczema severity (Eczema Area and Severity Index, EASI). Participant characteristics will be summarised using descriptive statistics and comparisons made between the different severity measures and treatments prescribed. Logistic regression will identify factors most strongly associated with referral from primary to secondary care. Phase 3 In-depth interviews with 20-30 purposefully sampled GPs will explore doctors' experience of managing children with eczema, in particular confidence in diagnosing and advising different treatments (including CAM), role of allergy testing, and reasons for referrals to secondary care. Interviews will be audio-recorded and transcribed verbatim. A thematic approach will identify the key themes and issues.

Supervisor(s):
In the first instance, enquiries should be directed to Dr Matthew Ridd (m.ridd@bristol.ac.uk).

Title: The origins of chronic obstructive pulmonary disease (COPD) in childhood

Outline: Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible by bronchodilators. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined criteria for diagnosis and staging of COPD and, based on these, a substantial proportion of young adults (20-44 years) has been reported to already have established COPD[1]. Cigarette smoking is recognized as a major risk factor for COPD but only a proportion of smokers develop the condition and there remains much to be learned about other factors that are important in the aetiology of COPD, with increasing interest focusing on early life events and their influence on lung and airway development. There is evidence from longitudinal studies that decrements in pulmonary function that are established in infancy and early childhood persist until adolescence. Failure to achieve maximal pulmonary function in early adult life is likely to be associated with increased respiratory morbidity as pulmonary function declines in later life and possibly with more rapid decrements in pulmonary function through mid-adulthood.

The aims of this project are to investigate the early life antecedents of having low values in adolescence (15-16 years) of FEV_1, maximal mid-expiratory flow (MMEF) reflecting small airways obstruction, and FEV_1/FVC ratio that are not bronchodilator-reversible. The research will be based in the Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal, prospective birth-cohort study recruited in pregnancy that has followed a population of nearly 14,000 children since birth. The primary outcome of this research will be post-bronchodilator pulmonary function measured in approximately 6000-7000 of this population at age 15+ years (MRC-funded G0401540). We will also apply methodology that we are successfully developing for the classification of wheezing phenotypes based on longitudinal modelling of wheezing symptom data to other respiratory symptoms, including reported cough during childhood. This work includes approaches to modelling data missing at random to maximize the power of the study to detect main effects and interactions between exposures.

Principal research questions of this research will address reports from observational studies of associations between COPD in adults and birth size, particularly focusing on markers of intrauterine growth restraint and subsequent growth during early childhood, and of the relationship between intrauterine and early life exposure to tobacco smoke and subsequent pulmonary function. We will also address novel hypotheses, including the association between maternal and early childhood diet (including antioxidant intake), distance of residence from main roads as a marker of traffic-related pollution exposure, and interactions between these variables and tobacco smoke exposure and irreversible airways obstruction in adolescence. We will also relate the lifetime history of asthma during childhood, including measures of bronchial responsiveness at 8 years, to pulmonary function outcome at 15-16 years to address the potential for some phenotypes of asthma to be associated with remodeling of airways and persistent deficits in pulmonary function. Although the proportion of the ALSPAC population that fulfils GOLD criteria for COPD is likely to be small at the age of 15-16 years, we anticipate that investigation of population traits of pulmonary function measurements to identify those in the lowest deciles of pulmonary function variables without evidence of bronchodilator-reversibility will make a valuable contribution to understanding the associations of early life associations with clinically important pulmonary outcomes. Also, given the richness of the data available in the ALSPAC study, analyses will be adjuster for a number of potential confounding and effects modifying variables, including socioeconomic status, parental history of pulmonary diseases and personal history of smoking validated by measurement of cotinine at 15+ years.

Reference:

1. de Marco R, Accordini S, Cerveri I, et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages *Thorax* 2004;59:120-125.

Supervisors: Dr John Henderson & Professor Jonathan Sterne

Title: Improving access to specialist CFS services by ethnic minorities and other disadvantaged groups

Background: Chronic Fatigue Syndrome or ME (CFS/ME) is a common, complex and disabling condition. Contrary to popular opinion, it appears to be more common in those from poorer socio-economic groups and in those from ethnic minorities. However, those that access specialist services are more likely to be from wealthier backgrounds and less likely to be from ethnic minorities.

Cultural factors are an important component on how people access health care. They may determine whether people seek health care, how they describe their condition, how their presentation is interpreted by health professionals and the treatment approaches they are willing to accept. Cultural factors may also act to increase risk factors that influence the aetiology and development of complex multi-factorial conditions including psychosocial factors such as social support, financial strain and mood disorders as well as biological factors such as genetic susceptibility and infections.

Objectives: Investigate whether cultural factors affect how those from ethnic minorities and other disadvantaged groups access specialist CFS support. Develop strategies to improve access for ethnic minorities and disadvantaged groups
Proposed methods: 1. Systematic review. 2. Qualitative study recruiting participants from: ethnic minorities and disadvantaged groups (including participants who have successfully accessed care and those who have been unable to access care); Health professionals (GPs and specialist services) and Community leaders working with ethnic minorities and disadvantaged groups. Participants who have CFS but have been unable to access care will be recruited form a trial investigating the early identification of CFS at GP level. 3. Use the results from the first two stages to develop an intervention to improve access to care by these groups.

Supervisor: Esther Crawley

Title: Causal inference in observational studies of substance use

Outline of Project

Background:

Multiple strands of evidence strongly suggest that substance use, of alcohol, tobacco and illicit drugs, is one of the most important environmental influences on health.[1 2 3] Substance use, however, tends to be socially patterned. People who use drugs are often different from people who don't in ways other than the fact of their substance use. These other differences may have profound implications for health that can complicate causal attribution in observational studies. Many types of substance use are associated with social disadvantage.[4 5 6 7] The challenge here is to differentiate between instances where substance use mediates the typical association between disadvantage and poorer health (suggesting one strategy to reduce health inequality) and others where the association between substance use and adverse health or social outcomes mainly reflects the fact that substance use is a marker for disadvantage that damages health through other pathways. Aside from an association with socials position, some types of substance use may reflect a tendency to take risks that again may influence health outcomes through multiple pathways, not all involving substance use. Moreover, aside from these issues of confounding, substance use is often subject to strong notions of social desirability that may influence how individuals report substance use to researchers.[7] All these problems mean that observational studies on the causes and consequences of substance use are fraught with methodological difficulties in terms of their usefulness as a basis for causal inference. These difficulties are often not acknowledged and strategies to overcome them are currently underdeveloped. A poor understanding of the causes of substance use is reflected in the limited success of prevention.[9 10 11 12 13] Parental substance use and childhood psychosocial problems, both exposures that are often more common amongst disadvantaged children, are widely held to be key influences on adolescent drug use.[14 15] Incomplete understanding of the consequences of drug use is illustrated by ongoing controversies such as whether cannabis use causes schizophrenia or influences educational attainment.[16] The Avon Longitudinal Study of Parents and Children (ALSPAC) is the UK's premiere resource for the study of the causes of the three commonest types of substance use (alcohol, tobacco and cannabis) and the short-term consequences of these behaviours amongst young people today. Crucially ALSPAC also provides the opportunity to investigate how problems such as confounding and reporting bias may complicate causal inference in this context.

Aim:

The aim of this studentship will be to illustrate how problems of confounding and reporting bias may compromise causal inference in observational studies of adolescent drug use and to develop strategies to overcome these problems.

Data:

Data will be obtained from ALSPAC, up to and including data collected in the age 15+ "Teen Focus 3" clinic and those obtained through linkage to the National Pupil Database. These data will include measures of pre and post-natal parental drug use, multiple measures of parental and family social position up to age 15, measures of childhood psychosocial and educational function, measures of self reported alcohol, tobacco and cannabis use from age 10 onwards and hair-based toxicological measures at age 15. Results from preliminary genome wide association studies on genetic predictors of key substance use phenotypes within an extensively phenotyped subset of the cohort will also be available. Data on educational performance in "Key stage 4" i.e. GCSE examinations will also be used.

Methods:

Building on previous work in ALSPAC at age 10, descriptive analyses will be presented on the prevalence of different substance use phenotypes at ages 13 and 15 and the distribution of

these according to measures of social position across the life course. Logistic regression analyses will then examine the association between different measures of parental drug use (for example both maternal and paternal use in the prenatal period and in early childhood) and measures of psychosocial function (such as conduct problems, bullying involvement, IQ and depression) with these later substance use outcomes. These analyses will be presented before and after measures of life course social position. Subsequent analyses will then examine the association between lifetime substance use up to age 15 and educational outcome at Key Stage 4. These analyses will compare effects of self-reported compared to toxicologically measured substance use and where possible will utilise any potential genetic instrumental variables identified through earlier GWAS studies. Again the influence of adjustment for life course social position on these effect estimates will be examined. It may be possible for students with a particular interest to develop more sophisticated statistical approaches to causal inference in this context such as those involving consideration of latent variables within structural equation or multilevel models.

Supervisor: John Macleod, Matthew Hickman.

Title: Modelling the transmission of Hepatitis C and HIV, and the impact of prevention strategies among injecting drug users in UK

Outline of Project:

Background:

Hepatitis C (HCV) and HIV cause substantial morbidity. In the UK 150,000 to 300,000 people are infected with HCV – over 80% due to injecting drug use; and nearly 10% of HIV cases are due to injecting. The epidemiology and evidence on the effectiveness of interventions are currently under review (NICE 2009, ACMD 2009).

Key findings are that in different settings in the UK there is variation in the prevalence of HCV/HIV amongst IDUs. Some of the variation in HCV prevalence is associated with homelessness and crack injection, but confusion still surrounds the link with syringe sharing - the main risk factor for spreading these viruses. The differences are likely to be partly due to reporting bias, but also may be due to subtleties in IDU syringe sharing behaviour that have not been recorded in previous surveys. Needle and syringe programmes (NSP) and opiate substitution therapy (OST) are the main intervention strategies for reducing HIV and HCV transmission. However, evidence on their intervention effect is weak, and there is little evidence on the levels of coverage of these and other interventions required to substantially reduce HCV or HIV.

This gap arises partly from limited evidence about what aspects of IDU risk behaviour determine the level of HCV and HIV transmission in different settings in the UK. In addition, there is limited understanding on how increased syringe distribution, or other forms of intervention contact may effect different IDU risk behaviours, such as the rate of syringe sharing, the size and stability of syringe sharing groups, and the degree of concurrent sharing. Without understanding these factors and relationships it is very difficult to evaluate the potential impact of different IDU focused interventions. Opportunities to develop better transmission models are arising because of new data and surveillance in the UK, including HCV Action Plan in Scotland (http://www.scotland.gov.uk/Publications/2006/09/15093626/0).

Aim:

To develop novel dynamic mathematical models of HCV and HIV transmission among IDUs in UK.

Data:

UK surveillance and enhanced surveillance data will be available (HPA 2008).

Methods:

Existing models of HCV and HIV transmission will be developed and used as the basis of this PhD (Vickerman 2006,2007). The new models will incorporate network structures, and will be developed in parallel with the collection of enhanced surveillance data in the UK that will attempt to understand better the intervention effect of NSP and OST.

References:

ACMD The prevention of hepatitis C among injecting drug users (Advisory Council on the Misuse of Drugs February 2009)

HPA Health Protection Agency, Health Protection Scotland, National Public Health Service for Wales, CDSC Northern Ireland, and the CRDHB. **Shooting Up: Infections among injecting drug users in the United Kingdom 2007**. London: Health Protection Agency, October 2008

NICE Needle and syringe programmes: providing injecting equipment to people who inject drugs. Expected publiation Febuary 2009
http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11829

Vickerman P, Hickman M, Judd A Modelling the impact on Hepatitis C transmission of reducing syringe sharing: London case study. Int J Epidemiol. 2007 Apr;36(2):396-405.

Vickerman P, Hickman M, Rodes T, Watts C. Model Projections on the Required Coverage of Syringe Distribution to Prevent HIV Epidemics Among Injecting Drug Users. JAIDS 2006; 42 (3): 355-361

Supervisors:
Peter Vickerman, Matthew Hickman

Title: Early exposure to environmental toxicants and parent-child relationship

Background

Environmental exposures in children continue to be a problem worldwide, even if in response to these exposures children present low body burdens of toxicants. For example, lead exposure is estimated to have a large impact on population IQ loss, and in young children is associated with a range of cognitive deficits, even at low blood lead concentrations (BLLs). Children's behavior is also affected by lead exposure, and preschoolers with elevated BLLs have been shown exhibit both externalizing and internalizing problems. Whereas the molecular mechanisms underpinning lead's effects on cognition and behavior in young children have received much attention, potential familial and behavioral mechanisms remain unexplored. It is possible that the quality of the developmental resources afforded by the home environment, like parent-child interactions, may exacerbate or buffer children's vulnerability to lead. To date, the home environment has largely been treated as a confounder, rather than a mediator or moderator in the relationship between BLL and neurobehavioral outcomes in children.

A small study of the mother-child relationship has revealed that when either the mother or her preschool child had BLLs $\geq 5\mu g/dL$, the mother was more likely to rate herself as having difficulty with setting limits or discipline. There is also evidence that elevated BLLs in adults are associated with irritability, fatigue and sleep disturbances, tension and depression. Adults with elevated body lead burdens also show deficits in executive functions, some of which (problem-solving, impulse control) are considered skills essential for parenting. Children with elevated BLLs show externalizing behaviors, inattention, social problems and executive function deficits. Because parent-child behaviors and relationships are transactional, it is plausible that not only will lead exposed children behave differently in interactions with their parents than non-exposed children, but that parents with elevated BLLs will exhibit different patterns of behavior towards their children. Surprisingly, there are no studies to help us understand the relationship among lead exposed parent-child dyads or triads.

Goal

The goal of this research is to understand how the family's exposure to lead affects their behavior and subsequently the child's neurobehavioral outcomes, and whether the family's interactions could serve as target for eventual behavioral intervention.

Methods

Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), the student will develop statistical analyses around the links between early exposure to lead (and other toxicants if desired) and parent-child relationships. Subsequent analyses may include functional outcomes in children, such as achievement of developmental outcomes, cognition and behavior and may draw upon structural equation modeling. The project may include use of data from questionnaires or direct observations of parent-child behaviors, and may incorporate other social or biological factors, such aspects of the social environment of the home or genetic underpinnings of behavioral traits.

Supervisors: Katarzyna Kordas, Yoav Ben-Shlomo

Title: Child obesity and the role of childcare settings: identifying risk factors and barriers/facilitators to reduce risks

Background:

By the time children start school, at age 4 to 5 in England, 13.2% are overweight and 9.4% are obese(1). The increased prevalence of overweight during infancy is of concern because it persists into later childhood and adulthood. The family environment is associated with a greater risk for obesity and the pre-school environment is one of the strongest predictors of physical activity. A Cochrane review of interventions to prevent obesity in children has identified prevention of obesity with young children as a priority area for further research (2).

Aims:

To inform the design of interventions to prevent obesity in preschool children, this study will identify risk factors for obesity associated with childcare settings; and identify barriers and opportunities for modifying the risks.

Objectives:

The thesis will explore a number of objectives using a range of methods. The objectives are:

1. To identify risk factors for child obesity.

2. To determine whether childcare settings during infancy are associated with adiposity in later childhood.

3. To determine whether childcare settings are associated with risk factors for obesity.

4. To identify barriers and facilitators to reduce the risk of obesity in preschool children in child care settings.

Design and methodology:

The objectives will be examined by:

(a) a review of systematic reviews of risk factors for obesity in preschool children

(b) a systematic review of childcare settings and risk factors for child obesity

(c) analysis of existing cohort studies (e.g. ALSPAC, MoBa and Generation R) for the associations of childcare setting and risk factors for obesity and adiposity in later childhood.

(d) a survey of parents and childcare providers to identify the presence of risk factors for obesity in childcare settings; the survey will be informed by observation of childcare settings and the literature reviews.

(e) a qualitative study using interviews with parents and childcare provider managers to identify barriers and opportunities for reducing known risk factors for obesity in preschool children.

Supervisors: Ruth Kipping & Russ Jago

10

Title: The decline and fall of obsolete medical technologies

Background:

Rogers identified seams of diffusion and discontinuance theory in anthropology, sociology, economics, communication, and marketing.1 Discontinuance of inefficient or inappropriately applied technologies will depend on characteristics of the technology (e.g. perceived relative disadvantage), characteristics of individuals who use it (e.g. training and receptiveness to change), systems within which they operate (e.g. financial incentives) and interactions among each component. Rogers distinguishes between replacement discontinuance, which occurs when more efficient technology displaces the existing technology (e.g. CT replacing skull radiography in head trauma) and disenchantment discontinuance, which results when new information indicates that the benefits of the existing technology do not justify the costs or adverse effects (e.g. withdrawal of rofecoxib due to evidence on an increased risk of cardiovascular events).

Discontinuance can be spontaneous or managed (i.e. disinvestment). Reliance on spontaneous discontinuance will fail if there are imperfections in the 'market' for health care. In particular, imperfect evidence about the costs, effects and safety of existing interventions or lack of communication of this evidence to clinicians and patients will delay optimal discontinuance. Antman et al2 reported that the majority of clinical experts recommended lidocaine for prophylaxis against ventricular fibrillation over a 25-year period despite successive trials showing no evidence of mortality reduction. Very little is known about the rate of health technology discontinuance or factors that facilitate it. In a review of more than 200 studies, Greenhalgh et al identified only one study that explicitly and prospectively studied discontinuance.3

Research methods & questions:

1. Use routine data sources (e.g. OPCS procedures and ePACT prescriptions data) to identify medical technologies that have rapidly declined in use in the last 10 years.
2. Purposively select case study technologies thought representative of rapid or protracted displacement or disenchantment discontinuance.
3. Conduct systematic reviews of the primary evidence (e.g. RCTs) and secondary sources (e.g. guidelines, policy statements) which may have led to the decline in use.
4. Interview clinicians (e.g. GPs, specialists), researchers (e.g. authors of seminal papers/guidelines) and policy makers to ascertain their views on the key factors causing or accompanying the decline.
5. Extend Rogers' theory of technology discontinuance to medical technologies and develop a taxonomy of facilitators and barriers to discontinuance.

References:

1. Rogers EM. Diffusion of Innovations. New York, NY: The Free Press, 2003.
2. Antman EM, et al. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 1992;268:240-248.
3. Greenhalgh T, et al. Diffusion of innovations in service organizations: systematic review and recommendations. Milbank Q 2004;82:581-629.

Supervisors:

William Hollingworth and Amanda Owen-Smith

11

Title: Air pollution and respiratory health in childhood

Background:
Exposure to high levels of atmospheric pollutants from traffic and non-traffic related sources is associated with a number of adverse health outcomes, including in the lungs and airways(1). We have modeled individual level exposures during pregnancy and early childhood for participants in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort.

Objectives and Plan:
This project will investigate the association of exposure to particulate pollution ($PM_{2.5}$) during prenatal and postnatal development with asthma, wheezing illness and lung function outcomes, which have been measured repeatedly during childhood. You will work in collaboration with air pollution experts at Imperial College London to derive different metrics of exposure and, under the supervision of Prof Henderson and Dr Granell, you will use these to model their associations with respiratory health throughout childhood. These analyses will address whether air pollution exposure at critical points of child development are associated with asthma or low lung function and will allow you to explore pathways that may mediate these associations, including birth weight and growth during childhood.

Proposed methods:
You will use modelled daily air pollution data derived at individual level for particulate (PM2.5) pollution using ADMS-Urban(2) and NAME models(3) at Imperial College London. You will learn to use a variety of statistical methods applied to longitudinal data analysis using Stata v.12 software, these will include linear, logistic and multinomial regression models as well as methods for dealing with missing data. Additionally there will be an opportunity to work in collaboration with international partners to study gene-environment interactions with air pollution exposure(4). This will involve genetic analyses of ALSPAC data and contributions to meta-analyses of pooled data from several different cohorts. Imputed genetic data is available for 10,000 children in ALSPAC and can be accessed from a Linux environment. Genetic analyses will be performed using available software specific to quantitative (mach2qtl) and binary (mach2dat) trait analysis.

Key references:

1. Kelly FJ, Fussell JC. Air pollution and airway disease. Clin Exp Allergy. 2011 Aug;41(8):1059-71.
2. CERC Ltd ADMS-Urban. An urban air quality management system. User Guide. 1999; Cambridge, CERC Ltd.
3. Ryall DB, Maryon RH. Validation of the UK Met Office's NAME model against the ETEX dataset. Atmos Environ 1998;32:4265-76.
4. Ji H, Khurana Hershey GK. Genetic and epigenetic influence on the response to environmental particulate matter. J Allergy Clin Immunol. 2012 Jan;129(1):33-41.

Supervisors: John Henderson, Raquel Granell

Title: Making Patient Reported Outcomes (PROs) from randomised controlled trials (RCTs) interpretable for clinicians to use in decision-making in surgical oncology

Background:
The has been an enormous increase in the use of PROs in RCTs over the past decade, but systematic reviews evaluating the impact of PROs from RCTs show that it is uncommon for the data to influence clinical decision-making [1-3]. There are several possible reasons for this observation. It is possible that PRO measures are not sufficiently sensitive to detect clinically relevant outcomes in trials or that trials with PROs are poorly designed and therefore PROs cannot influence clinical making because data are unreliable and bias. Another reason for this finding is that clinicians do not understand and are not familiar with PROs and the data they yield[4]. Clinicians may not appreciate how changes in PROs translate into meaningful outcomes and there is uncertainty about how to combine clinical and PROs from trials to influence decisions. Some recent work has suggested that by separating the analysis and data presentation from trials from the interpretation within a clinical setting this will improve clinician understanding and therefore use of PROs from RCTs to influence clinical decision-making [5].

Therefore, the focus of the proposed PhD is to explore how PROs from RCTs may be analysed and presented to clinicians and it will evaluate methods for interpreting clinical and PROs from RCTs together. Finally it will evaluate how the data are used in practice (in teams and in out patient consultations), with the ultimate aim of improving the interpretability of PROs from RCTs to use in clinical practice.

Aim:
To analyse PROs from RCTs and explore methods of presenting and interpreting the data to use by clinical teams and in patient consultations during treatment decision-making.

Methods

- Systematic literature review to summarise presentation methods of PROs from RCTs
- Selection of ongoing/completed trials to act as studies to analyse PRO data and present the results in multiple formats
- Use qualitative methodology to interview professionals with a selection of PRO analyses to consider clinical interpretation of the findings
- Use non-participant observation of consultations and clinical teams to consider how PROs are used in practice to influence decisions

References

[1] Blazeby JM, Avery K, Sprangers M, Pikhart H, Fayers P, Donovan J. Health-related quality of life measurement in randomized clinical trials in surgical oncology. *J Clin Oncol* 2006; 24(19):3178-3186.

[2] Efficace F, Bottomley A, van Andel G. Health related quality of life in prostate carcinoma patients: a systematic review of randomized controlled trials. *Cancer* 2003; 97(2):377-388.

[3] Efficace F, Bottomley A, Vanvoorden V, Blazeby JM. Methodological issues in assessing health-related quality of life of colorectal cancer patients in randomised controlled trials. *European Journal of Cancer* 2004; 40:187-197.

[4] Guyatt G, Schunemann H. How can quality of life researchers make their work more useful to health workers and their patients? *Quality of life Research* 2007;16:1097-1105

[5] Making quality of life results more meaningful for clinicians. *Lancet*; 2008:709-710.

Primary supervisor: Prof Jane M Blazeby, School of Social Medicine & University Bristol Hospitals NHS Foundation Trust.

Secondary supervisor: Dr Sara T Brookes, School of Social & Community Based Medicine

Title: Diurnal patterns of physical activity, sedentary behaviour, heart rate and blood pressure in adolescents

Description:

Relatively little is known about the determinants or consequences of different patterns of 24-hour change in blood pressure (BP) in healthy adolescents. There are a number of methodological challenges to simultaneously modeling change data for different measurements, but the potential value of being able to do so is increasingly recognized. The availability of detailed data on 24-hour monitoring of BP and accelerometer assessed activity in healthy 17-18 year olds, together with a wealth of additional data in this birth cohort, provides a unique opportunity to address these gaps.

Below are a number of potential objectives. These are likely to cover more than one distinct PhD. We would anticipate students studying in depth 1-3 of the objectives and indeed adding their own areas of interest in relation to the broad topic of diurnal patterns of physical activity and/or blood pressure in adolescence.

1. To describe diurnal patterns of accelerometer assessed physical activity, sedentary behavior, SBP, DBP and heart rate in healthy 17-18 year olds, measured using 24-hour continuous monitoring.
2. To examine the association of diurnal patterns of accelerometer assessed physical activity and sedentary behaviour with diurnal patterns of SBP, DBP and heart rate.
3. To describe diurnal patterns of central (aortic) BP and compare this with diurnal patterns of peripheral (brachial) BP.
4. To examine whether diurnal variability in BP is associated with other cardiovascular risk factors independently of mean level of BP
5. To examine whether 'dipping' (change in BP between day and night time) is associated with other cardiovascular risk factors independently of mean level of BP
6. To examine the associations of change in weight and height from birth to 17 years and fat and lean mass from 9-17 years with diurnal patterns of SBP, DBP and heart rate at age 17-18
7. To examine the associations of change in physical activity and sedentary behaviour (accelerometer assessed) from age 11-17 with diurnal patterns of SBP, DBP and heart rate at age 17-18
8. To examine the association of hypertensive disorders of pregnancy and change in maternal BP in pregnancy with diurnal patterns of SBP, DBP and heart rate at age 17-18
9. To examine whether genetic variants associated with differences in BP in adults are associated with different diurnal patterns of BP in adolescents

For more information about the actual PhD project (as opposed to adim. Student issues) contact Debbie Lawlor – d.a.lawlor@bristol.ac.uk

Supervisors:

There are a number of potential phd projects for this proposal from the very statistical methodology to the much more applied.

Depending on the particular focus of the project supervision would be by 2 or 3 of the following:

Prof Kate Tilling, Dr Laura Howe (University of Bristol), Dr Abi Fraser, Dr Corrie Macdonald-Wallis, Prof Debbie Lawlor

The work will be done in collaboration with colleagues in Imperial (London) and one of either Prof Alun Hughes or Prof Nish Chaturvedi from Imperial will provide additional supervision, in particular on the clinical relevance and meaning of some of the measurements.

Title: The Cognitive Neuroscience of Developmental Simultagnosia

Aim :
Tto provide a detailed behavioural and neural characterisation of developmental simultagnosia.

Background:
In adults a visual impairments in the ability to extract information from a cluttered visual scene following brain damage is called simultagnosia. Simultagnosia often follows bilateral damaged to the parietal lobes and is described as part of Balint's syndrome. Increasingly this problem is also being recognised in children, who present with difficulties in learning to read and write and other behavioural problems such as being abnormally overwhelmed by crowded environments. At present there are few clinical tools to identify and quantify this problem and therefore there is little evidence about the natural history of the condition, the neural basis of it, or the effect of interventions used to support affected children.
The aim of this work is to provide a detailed characterisation of the condition using behavioural testing, includinging the objective measures of eye movements and to carry out Structural and functions MRI imaging studies of the children to identify the changes in brain function and structure that characterise the condition

Methods:
Children aged 5 – 16 will be recruited from various sources including the large cohort of such patients seen in Bristol Eye Hospital. These children will be already suspected of having difficulties extracting information from a cluttered scene and will then have formal assessment to quantify to what extent this is the case using adapted tests from adult neuropsychology. Age- and sex- matched children will also be recruited who have no suspected visual perceptual disorders and they will be given the same assessment. Visual acuity, ocular alignment, stereopsis and refractive error will also be tested (or obtained from medical notes).
To understand in more detail why these children have a particular problem with cluttered environments, all recruited children will have objective eye movement recordings made when performing visual search tasks. The equipment to be used does not require any form of head restraint or chin rest and so will be suitable for use with these children. Specific parameters to be measured will include the number of fixations required to find a target and the duration of these fixations, saccade amplitude and characteristics (for example the main sequence). These variables will provide a robust quantitative description of the child's eye movement performance whilst looking at a target display.
We will also carry out structural MRI to investigate if specific areas of these children's brains differ from the controls (one candidate is white matter density in the parietal lobe) and carry out Diffusion Tensor Imaging (DTI, which allows white matter tracts within the brain to be imaged) using MRI to quality the changes in connections that may characterise the condition. This work will be carried out at the new Bristol Clinical Research and Imaging Centre (www.cricbristol.ac.uk)
For further information, contact cathy.williams@bristol.ac.uk

Supervisors: Dr Cathy Williams, Centre for Child and Adolescent Health, School of Social and Community Medicine & Professor Iain Gilchrist, School of Experimental Psychology, http://eis.bris.ac.uk/~psidg/homepage.html

Title: Early life inequalities in asthma: estimating its burden and understanding its aetiology

Outline of the project:

Background: Asthma is associated with a considerable disease burden. Asthma prevalence varies across time,[1] geographical regions and socioeconomic conditions[2] but the reasons for these variations are not well understood. The direction and magnitude of socioeconomic inequalities in asthma is important not only to quantify an inequitable burden of this condition in subgroups of the population but understanding the mechanisms that give rise to them can help to identify potential causal exposures. Real changes in the socioeconomic distribution of exposures, early reporting and detection bias, differential health service use, grouping of distinct asthma phenotypes, and/or to differences in the socioeconomic indicators used can all contribute to these variations.

It has been long recognized that asthma is a complex heterogeneous disease. One key aspect of this project will be to describe the burden and magnitude of life course inequalities in distinct asthma phenotypes newly described in ASLPAC[3,4] and to identify the exposures that drive them. Deprivation related to wheezing at 6 months in ALSPAC children[5] and their parents.[6] Longer follow-up, a wider array of socioeconomic indicators, specific asthma phenotypes and including health services use and social selection will provide thorough evidence of these initial findings. Poorer socioeconomic conditions were only or more strongly associated with a phenotype of transient asthma in a birth cohort from Pelotas,[7] and with prolonged early wheeze in ALSPAC (preliminary results), providing support to the hypothesis that different asthma phenotypes are differentially patterned. This is likely to relate to different socioeconomic distribution of exposures.

Exposures amenable to prevention acting throughout the life course have been related to asthma. These include, maternal diet, pregnancy weight gain, pregnancy–induced hypertension, smoking, stress and maternal alcohol consumption, breastfeeding, post-natal gut colonisation, environmental tobacco smoke, low birth weight, growth, respiratory infections, hormonal levels, pet ownership, domestic heating, damp and mould in the house, other allergen exposure, child's diet and obesity, drug use, smoking and occupational exposures.

Objectives:

1. Systematically review the evidence of inequalities in childhood asthma and its variation (in direction and/or magnitude) over time and geographical regions.
2. Describe the direction and magnitude of inequalities in ALSPAC children using detailed phenotypic definitions.
3. Identify potential exposures that can explain the inequalities pattern and therefore help preventing the unequal burden of disease and understand mechanisms of the disease.

The above objectives are likely to cover more than one distinct PhD. Different students can evaluate in depth objectives 1 and 2 and focus on different environmental exposures, according to their own personal interests, for objective 3.

Data and Statistical Methods:

Analyses will be based on data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population-based birth cohort study, which recruited 14,541 pregnant women in 1990/91[8] (http://www.alspac.bris.ac.uk). Alspac has extensive measures of asthma phenotypes obtained at different points in time from birth to age 9: wheezing phenotypes up to seven years; asthma, hay fever, eczema, skin test reactivity, blood total IgE at 7 years; and lung function and bronchial responsiveness at 8-9 years. Blood cotinine at age 8. Numerous prenatal and postnatal potential risk factors or confounders are available. Extensive obstetric data is available from the mothers. Biological specimens include placenta, umbilical cord, milk teeth, hair, urine, repeat blood samples, and clinic measures include anthropometry, blood pressure, cardiac ultrasound, endothelial function, pulse wave velocity, physical fitness

and up to three weeks of objective physical activity monitoring. DNA has been collected from mothers and at multiple time points from children. An extensive list of indicators of SEP measured at different time points are available as well as measures of health services utilisation.

Students will use appropriate statistical techniques to the specific objectives, including regression models and instrumental variables analyses (e.g. for Mendelian randomization approaches using genetic variants as instrumental variables to establish causality between exposures of interest and asthma (Objective 3)).

References:

1. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. The Lancet 2006;368:733-43.

2. Braback L, Hjern A, Rasmussen F. Social class in asthma and allergic rhinitis: a national cohort study over three decades. Eur Respir J 2005;26:1064-8.

3. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax 2008;63:974-80.

4. Henderson J, Granell R, Sterne J. The search for new asthma phenotypes. Arch Dis Child 2009;94:333-6.

5. Baker D, Taylor H, Henderson J. Inequality in infant morbidity: causes and consequences in England in the 1990s. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Epidemiol Community Health 1998;52:451-8.

6. Baker D, Henderson J. Differences between infants and adults in the social aetiology of wheeze. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Epidemiol Community Health 1999;53:636-42.

7. Muino A, Menezes AM, Reichert FF, Duquia RP, Chatkin M. [Wheezing phenotypes from birth to adolescence: a cohort study in Pelotas, Brazil, 1993-2004]. J Bras Pneumol 2008;34:347-55.

8. Golding J, Pembrey M, Jones R, The Alspac Study Team. ALSPAC-The Avon Longitudinal Study of Parents and Children. Paediatric and Perinatal Epidemiology 2001;15:74-87.

Supervisor:

Dr Bruna Galobardes, School of Social and Community Medicine, CAiTE

Title: Stress responses in obesity

Project Outline:

Obesity is a major and growing public health concern. The latest WHO projections indicate that at least one in three of the world's adult population is overweight and almost one in 10 is obese. Being overweight or obese can have a serious impact on health with serious health consequences such as cardiovascular disease (mainly heart disease and stroke), type 2 diabetes, musculoskeletal disorders eg osteoarthritis, and some cancers (endometrial, breast and colon). These conditions cause substantial disability and premature death.

Risk of health problems starts when someone is only very slightly overweight, and the likelihood of problems escalates as BMI increases. Many of these conditions cause long-term suffering for individuals and families. In addition, the costs for the health care system are extremely high.

Whilst eating is essential, overeating can be seen as an abnormal behaviour governed by many factors. One explanation is that abnormal stress responses have a significant role and this PhD will look at this in depth. Previously it has been difficult to model stress. We have developed a paradigm that involves inhalation of either a single breath of 35%CO2 or 15 minutes of a 7.5% CO2/air mixture. This activates the key stress responses including the hypothalamo-pituitary- adrenal axis (increasing cortisol), the autonomic nervous system (increasing blood pressure and heart rate) and behavioural activation (increases anxiety). It is likely although not proven that this model also activates the pro-inflammatory cascade. This is potentially important as obesity is associated with chronic low grade inflammation and this in turn can have effects on serotonin neurotransmission which is known to be important in both regulating feeding behaviour and emotional tone. This project will have 3 major areas. The candidate will review the literature on stress responses in obesity and then assess stress sensitivity using the CO2 paradigm in obese patients and age/sex matched controls. Patients will be recruited from Dr Andrews large cohort in Taunton's Musgrove Park Hospital. The effect of treatments (including behavioural interventions, exercise, medication, bariatric surgery etc) on all the above stress responses will be assessed and changes in stress response with respect to outcome will also be measured. The exact nature of the studies will be developed by the candidate with guidance from the supervisors.

Supervisors: Dr John Potokar Senior Lecturer in Psychiatry
Dr Rob Andrews Senior Lecturer in Endocrinology

17

Title: Legal, Ethical and Clinical Dilemmas at the End of Life

Project Outline:

Care at the end of life continues to generate numerous legal, ethical and clinical dilemmas for patients, professionals and society at large. Phenomena like "assisted suicide tourism", in which British citizens have travelled abroad for assistance in suicide, raise new questions for lawyers and policymakers in particular, whilst clinicians continue to grapple with the problems associated with symptom relief and appropriate care for the dying patient. The approaches taken in these disputed areas are themselves contested, from a variety of ethical perspectives premised on different accounts of the value(s) of human life.

Applications are invited for a well-specified PhD project that falls within the broad subject area outlined here, and which particularly engages with both the legal/(bio)ethical *and* the clinical dimensions of death and dying. Applicants are encouraged to include both a theoretical *and* an empirical component to their proposed study (with an appropriate justification of the methodological links between the two), although a purely theoretical exploration may be warranted (provided there is sufficient justification for the proposed study and approach, and clear relevance to clinical practice). Applicants may also wish to incorporate a comparative element to their proposed study (e.g. comparing different medical specialties, or different countries/jurisdictions).

Supervisor: Dr Richard Huxtable, Senior Lecturer/Deputy Director, Centre for Ethics in Medicine

Title: Risk factors for depression in adolescence

Project Outline:

Applications are invited from suitably qualified graduates to join a team investigating risk factors associated with the development of depression during adolescence. The PhD will be undertaken in the School of Community Based Medicine with Dr Carol Joinson and Professor Ricardo Araya.

Depression is a common condition affecting around 2-3% of children and 5-8% of adolescents in population samples. Community studies suggest an increased rate of children being diagnosed with depression, and for diagnosis to occur at earlier ages.

There is strong evidence from both clinical and community studies that the onset of depression in late childhood and early adolescence has a chronic and recurrent course. In particular, early depression substantially increases the risk of future adverse outcomes including impaired social functioning, low academic achievement, anxiety, substance abuse and suicidal behaviour. Adolescents with depressive symptoms that do not meet full diagnostic criteria for a mood disorder still show elevated risks for later depression, and corresponding impairments in psychosocial functioning, greater risk for health service utilization and other symptoms such as hopelessness and suicidal behaviours.

Emergence and persistence of depressive symptoms in early life could therefore represent important warning signs of persistent problems throughout life. Given the severe consequences associated with depression there is a need for systematic longitudinal research to provide a better understanding of how depressive symptoms develop in childhood and adolescence and the factors that influence the risk for depression.

The main focus of the research will be to examine how environmental risk factors including socioeconomic disadvantage and stressful life events interact with individual characteristics including temperament, personality and timing of puberty to influence the risk for depression in adolescence.

The project will take advantage of the unique and extensive longitudinal data collected by the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing longitudinal population-based study investigating a wide range of environmental and other influences on the health and development of children. Detailed information on the ALSPAC study is available on the web site: http://www.alspac.bris.ac.uk

Supervisors: Dr Carol Joinson and Dr Jon Heron

Title: Early Temperament and Vulnerability to Depression in Adolescence: The Role of Parenting and Parental Characteristics

Background:

Adolescence is characterised by a marked increase in depression. Lifetime prevalence of major depression in 15-18 year olds in a nationally representative survey in the US was 14%, with an additional 11% reporting minor depression [1]. Approximately 25-40% of adolescents exhibit high levels of depressed mood [2]. Depression has a chronic and recurrent course and substantially increases the risk of future adverse outcomes including impaired social functioning, lower academic grades, anxiety, unwanted pregnancies, substance abuse and suicidal behaviour [3]. Given the severe consequences associated with depression there is a need for systematic longitudinal research to provide a better understanding of the factors that influence the risk for depression. There is growing evidence that temperament traits in early childhood, including high reactivity of the 'withdrawal' system (related to shyness/fear) and low reactivity of the 'approach' system (related to sociability and positive affect), may increase risk of depression in adolescence [4-6]. Although underlying temperament traits may be associated with vulnerability for internalizing problems, other factors must co-occur for depression to develop [4]. This is consistent with a vulnerability / stress-diathesis model, with underlying temperament as the diathesis [7].

From the perspective of a vulnerability model, a vulnerable temperament must be accompanied by adversity for depression to develop [8]. Prior research has found a strong association between emotional symptoms and parent-child relationships [9-12], and this relationship is modified by the child's temperament [13]. Children with vulnerable temperament who are exposed to certain parenting styles or parent characteristics, including low nurturing, high discipline, parental discord and parental psychopathology, may be at increased risk of depression in adolescence[14-16]. However, there are methodological limitations to previous studies including relatively small sample size and cross-sectional design [3]. There is a lack of longitudinal research in large representative cohorts to provide a better understanding of how child temperament interacts with parenting style and parent characteristics in the development of depression in adolescence [17-19].

Study Objectives:

This study will use data from a large UK cohort- Avon Longitudinal Study of Parents and Children (ALSPAC), which includes measures of temperament in early childhood and internalizing problems from childhood to late adolescence. Examining these measures of early temperament and internalizing problems together with parenting measures from infancy onwards would allow identification of pathways to increased risk of depression in adolescence. The main aim of the proposed project is to examine the role of parenting style and parent characteristics on the relationship between early temperament and development of depression in adolescence. The project will test the hypothesis that there is an interaction between parenting variables and temperament on levels of depression/depressive symptoms in adolescence. Specifically, the proposed project will examine whether the effect of vulnerable temperament traits, including high reactivity of the 'withdrawal' system and low reactivity of the 'approach' system, on the development of depression/depressive symptomatology is enhanced in adolescents where there is evidence of parent-child conflict, low nurturing/affection and low emotional support. The potential role of parental discord and parental mental health problems in enhancing the risk of depression in children with vulnerable temperament traits will be examined. The study will also examine whether certain parent factors (including praise, emotional support, warmth and engaging in activities with the child) have a protective effect on development of internalizing problems in children with vulnerable temperament. Analyses will also examine the role of gender, parental mental health, indicators of family socio-economic background including socio-economic status (SES), parental education and financial problems, and previous levels of internalising

problems before adolescence (measured by the SDQ [20] and DAWBA [22]) in the association between temperament and depressive symptoms.

References:

1. Kessler, R.C. and Walters, E.E. 1998. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depression and Anxiety.* 7: 3-14.
2. Petersen AC, Compas BE, Brooks-Gunn J, Stemmler M, Ey S, Grant KE. Depression in adolescence. Am Psychol. 1993 Feb;48(2):155-68. Review.
3. Hammen C. and Rudolph, K. D., 2003. 'Childhood Mood Disorders' in E. J. Mash and D.J.A. Dozois (eds), *Child Psychopathology. 2nd Edition.* New York: The Guilford Press.
4. Nigg JT. Temperament and developmental psychopathology. Journal of Child Psychology and Psychiatry 2006;47(3/4):395-422.
5. Watson D, Gamez W, Simms LJ. Basic dimensions of temperament and their relation to anxiety and epression: A symptom-based perspective. Journal of Research in Personality 2005;39:46-66.
6. Oldehinkel AJ, Hartman CA, De Winter AF, Veenstra R, Ormel J. Temperament profiles associated with internalizing and externalizing problems in preadolescence. Development and Psychology 2004;16(2):421-40.
7. Ingram RE, Luxton DD. Vulnerability stres models. In: Benjamin L.Hankin JRZA, editor. Development of psychopathology: a vulnerability-stress perspective. SAGE, 2005; 2005. p. 32-46.
8. Pulkinnen L, Caspi A. Personality and paths to successful development: An overview. Paths to successful development: Personality in the life course. Cambridge University Press; 2002. p. 1-16.
9. Patton G, Olsson C, Bond L, Toumbourou J, Carlin J, Hemphill S et al. 2008. Predicting female depression across puberty: a two-nation longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 47:1424-31.
10. Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc Natl Acad Sci U S A 2006 February 28;103(9):3480-5.
11. Blanz, B., Schmidt, M., & Esser, G. (1991). Familial adversities and child psychiatric disorders. Journal of Child Psychology and Psychiatry, 32, 939–950.
12. Resnick M, Bearman P, Blum R, Bauman K, Harris K, Jones J et al. 1997. Protecting adolescents from harm: findings from the National Longitudinal Study on Adolescent Health. *JAMA*; 278:823-32.
13. Oldehinkel AJ, Veenstra R, Ormel J, De Winter AF, Verhulst FC. 2006. Temperament, parenting, and depressive symptoms in a population sample of preadolescents. *J Child Psychol Psychiatry*. July;47(7):684-95.
14. Lovejoy, C.M., Graczyk, P.A., O'Hare, E., and Newman, G. 2000. Maternal depression and parenting behaviour: a meta-analytic review. *Clinical Psychology Review. 20: 561-592.*
15. Radke-Yarrow, M. (1998). Children of depressed mothers: From early childhood to maturity. New York: Cambridge University Press.
16. Lengua, L.J., West, S.G., & Sandler, I.N. (1998). Temperament as a predictor of symptomatology in children: Addressing contamination of measures. Child Development, 69, 164–181.
17. Kessler R, Avenevoli S, Merikangas K. 2001. Mood disorders in children and adolescents: an epidemiologic perspective. *Biological Psychiatry* 49:1002-14.
18. Roberts, R.E., Attkisson, C.C. & Rosenblatt, A. 1998. Prevalence of psychopathology among children and adolescents. *American Journal of Psychiatry.* 155: 715-725.

19. Sentse M, Veenstra R, Lindenberg S, Verhulst FC, Ormel J. Buffers and risks in temperament and family for early adolescent psychopathology: generic, conditional, or domain-specific effects? The trails study. Dev Psychol. 2009 Mar;45(2):419-30.

Supervisors: Dr. Carol Joinson, Dr Jon Heron

20

Title: Different methods of dietary patterns and their associations with bone development in childhood and adolesence

Background:
Several studies have found positive associations between greater bone mineral density (BMD) and increased consumption of various dietary factors including potassium, magnesium and fruit and vegetables. However, due to the complexity of the foods and nutrients we eat and the inter-correlations between them, it is also important to assess the diet as a whole. Dietary patterns enable the assessment of the overall diet and may provide additional answers to the analysis of individual foods and nutrients.

Setting:
The project will take advantage of the unique and extensive longitudinal data collected by ALSPAC. Detailed information on the ALSPAC study is available on the web site: http://www.alspac.bris.ac.uk

Data:
Bone density has been collected via DXA scan at 9, 11, 13, 15 and 17 years of age. In addition. pQCT scans which assess volumetric density have been performed at 15 and 17. Three-day diet diaries were collected at 7, 10 and 13 years of age.

Aims:
The main focus of this research will be to investigate the different methods of obtaining dietary patterns, focussing on Principal Components Analysis, Cluster Analysis and Reduced Rank Regression in determining optimum bone development in the ALSPAC cohort. In addition the performance of each method in predicting bone density will be tested.
Fat mass and physical activity have been shown to affect skeletal development in childhood; this project will further examine whether any effects of dietary patterns on bone development are mediated by altered body composition and activity levels.

Supervisors: Kate Northstone, Jon Tobias

Title: Optimising informed consent processes during recruitment to Randomised Controlled Trials (RCTs): a mixed methods investigation.

Proposal:
This would be a three- or four-year studentship to apply mixed methods to investigate how to optimise the informed consent processes that take place during recruitment to RCTs.

Background

Recruitment to randomised controlled trials (RCTs) is notoriously difficult. There is evidence that the quality and quantity of communication discussion between the clinician and the patient impact on patient decisions about whether to participate (Albrecht et al. 2008). Evidence shows that patient understanding about trial procedures and treatments may be less than optimal, at the time of decision-making about trial participation, and a systematic review of measures to improve understanding suggests that understanding can best be achieved by face-to-face discussion (Flory & Emmanuel, 2004). Yet recruiters may find it difficult to convey key RCT concepts (e.g. clinical equipoise and randomisation) in a way that patients readily understand (Paramasivan et al. 2011), provide imbalanced information about treatment (Donovan et al. 2002) or fail to elicit and explore patient preferences or concerns (Mills et al. 2011, Wade at al.2009).

Professor Jenny Donovan leads a programme of research within the MRC funded ConDuCT (Collaboration and innovation in Difficult and complex randomized Controlled Trials) hub to develop interventions to maximise levels of recruitment and informed consent in difficult trials. This work includes the development of a novel model to facilitate informed consent at trial recruitment (Wade et al. 2009) and an investigation of how exploration of patient treatment preferences can facilitate trial recruitment (Mills et al. 2011).

Objectives

- Conduct a systematic review of the literature on informed consent, including in particular the practical and ethical issues relevant to informed consent in randomised controlled trials
- Apply a novel measure, developed to evaluate the content and quality of informed consent discussions during recruitment consultations, to recruitment discussions from up to eight RCTs with a view to evaluating the tool in terms of validity, reliability and use in the training of recruiters.
- Explore the application of the measure to routine practice in taking informed consent for procedures/investigations outside of the trial context.

Proposed methods

The proposed study will involve mixed methods, combining qualitative and quantitative method to evaluate recruitment discussions. Qualitative methods of analysis will include content, thematic, and conversation analysis. Quantitative methods of determining validity and reliability in the development of new health measurement scales (Streiner & Norman 2008), will be used to evaluate the new measure and determine its value as a tool to improve the content and quality of information provided by recruiters, and patient understanding of that information.

You will benefit from working within a team, which has built up considerable expertise in this area. This topic will suit a candidate looking to gain mixed methods experience in conducting systematic reviews, and applying qualitative research and quantitative methods to investigating health professional-patient interaction both during trial recruitment and more generally and the goal of the research will be to identify ways of improving patient experience. The successful applicant will be based at the School of Social and Community Medicine (formerly School of Social Medicine and Community Based Medicine). The School hosts the ConDuCT Hub (Collaboration and innovation in Difficult and complex randomized

Controlled Trials), funded by the MRC, which has been established to provide a regional focus for high-quality, cutting-edge methodology research in randomised clinical trials and from April 2014 will host ConDuCT II (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures). The successful applicant will work within the MRC funded ConDuCT hub for clinical trials methodology research. The School has experience of conducting a number of studies investigating trial processes and procedures using qualitative methods, with a view to identifying potential improvements (e.g. Donovan et al. 2002, Mills et al. 2011, Wade et al. 2009).

Contact: Dr Julia Wade or Professor Jenny Donovan

References/suggested reading:

Mills N**,** Donovan JL, Wade J, Hamdy FC, Neal DE, Lane JA. Exploring treatment preferences facilitated recruitment to randomised controlled trials. *J Clin Epidemiol* 2011; 64: 1127-1136.

Paramasivan S**,**Huddart R**,** Hall E**,** Lewis R**,** Birtle A, Donovan JL. Key issues in recruitment to randomised controlled trials with very different interventions: a qualitative investigation of recruitment to the SPARE trial. *Trials* 2011; **12**:78 (doi:10.1186/1745-6215-12-78)

Donovan JL**,** Lane JA, Peters TJ, Brindle L, Salter E, Gillatt D et al for the ProtecT Study Group. Development of a complex intervention improved randomization and informed consent in randomized controlled trials. *J Clin Epidemiol* 2009; 62:29-36.

Donovan JL, Lane JA, Peters TJ, Brindle L, Salter E, Gillatt D et al for the ProtecT Study Group. Development of a complex intervention improved randomization and informed consent in randomized controlled trials. *J Clin Epidemiol* 2009; 62:29-36.

Wade J, Donovan JL, Lane JA, Neal DE, Hamdy FC. It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials. *Soc Sci Med* 2009; 68:2018-28.

de Salis I, Tomlin Z, Toerien M, **Donovan J**. Qualitative research to improve RCT recruitment: issues arising in establishing research collaborations. *Contemporary Clinical Trials* 2008; 29: 663-70.

de Salis I, Tomlin Z, Toerien M, **Donovan J**. Using qualitative research methods to improve recruitment to randomized controlled trials: the Quartet study. *J Health Serv Res Policy* 2008; 13: 92-6.

Streiner DL & Norman GR *Health Measurement Scales: A practical guide to their development and use*. (2008) OUP: Oxford, UK.

Supervisors: Julia Wade and Jenny Donovan

Title: Digit ratio, development, gender orientation and disease.

Proposal:

The ratio of the length of the ring finger relative to the index finger (popularly known as either the finger ratio or digit ratio) has been studied extensively in the psychological and physical anthropological literature. i It is considered to reflect intra-uterine sex-hormone exposure, and also has clear genetic influences. We have recently demonstrated a common genetic variant, that had previously been related to age at puberty, predicts finger ratio (Meados et al, in press) in a study combining ALSPAC and QIMR Brisbane Adolescent Twin study data. Previous investigations of the associations of finger ratio with a wide range of phenotypes have reported a comprehensive list of relationships, from birth dimensions, growth trajectories, adiposity, height, fertility, neurodevelopment, handedness, autism, attention deficit, skin colour to a variety of disease states including asthma, number of colds, various infections, etc, and in particular gender orientation. The studies have tended to be based on small and unrepresentative samples with limited phenotyping. This PhD would complete the most comprehensive examination to date of such associations in the ALSPAC and QIMR Twin studies.

ALSPAC, a birth cohort started in the early 1990s, has obtained extensive data from before birth through to age 17 on a large population-based sample. Finger ratio was measured at a clinical examination and extensive information, often taken on repeat occasions, are available on gender orientation (including the Bem Index and a wide range of additional questions regarding play styles and sexual relationships), growth from birth onwards, age at puberty, autism spectrum, handedness, attention deficit, intelligence, physical fitness. Genome wide data have already been obtained on a sub-sample of the cohort and are now being completed on the entire cohort as well as on the mothers, which allows analysis of maternal genotype in relation to a phenotype which reflects intrauterine development. In the QMIR Twin study twins are recruited at primary school and have been followed up through to age 19 to date, with over 5,000 adolescents from more than 1,500 families having participated. Data on a wide range of physical and psychological traits have been collected. Many traits have been collected at multiple time points allowing for longitudinal analyses focusing on developmental change. In addition, because data have been collected from both twins and all available siblings this sample provides a powerful resource for genetically informative analysis. The sample has also been extensively genotyped both for linkage (STR markers) and association (Illuminia 610K snp chip). Analysis of data from these two studies and producing a series of reports on these analyses, together with thinking through future directions of research in this area, would be of the focus of the PhD.

Supervisors: George Davey Smith, Sarah Meddows, Marcus Munafo.

(i) Manning J. The finger ratio. Faber and Faber London, 2008.

Title of the project: What is the effectiveness of 'real world' delayed antibiotic prescribing and can "ScriptSwitch" increase its use?

Background:
The 'delayed antibiotic' strategy is most frequently used in primary care and may be described as the clinician (GP or Nurse Practitioner, NP) giving the patient a prescription but advising it is not 'cashed' at a pharmacy or consumed for a few days in the hope that the patient's underlying infection symptoms improve and the antibiotic is no longer needed. It has been shown to be a safe and an effective method to reduce overall antibiotic consumption for a range on conditions including chest infections (children and adults),[1] sore throat (adults),[2] ear infections (children),[3] conjunctivitis[4] and urinary tract infection (adults only).[5] However, nearly all the data on the effects of delayed antibiotic prescribing is from the efficacy studies in which it was evaluated.
ScriptSwitch is the UK's leading provider of prescribing decision support and is currently used by Bristol Clinical Commissioning Groups (CCGs, see http://www.scriptswitch.com/). In essence, it is an automatic 'pop up' that appears on GPs electronic medical record systems to alert the GP/NP to a prescribing option different to that which they were about to select. In the case of an antibiotic, it could be programmed to ask the GP/NP to consider issuing a 'delayed antibiotic' prescription.
Aim: To investigate the real world 'pragmatic' effects of delayed antibiotic use and test if 'ScriptSwitch' could be used to increase its use.

Objectives:

1. To review the literature (and update any relevant systematic reviews) regarding the effectiveness of delayed prescribing on cashing of prescriptions, antibiotic consumption and subsequent health care consultations
2. To review the evidence for the variations in the ways is it currently used and the relationship between these varying characteristics and its effectiveness
3. To use an existing data set (TARGET (see http://www.targetstudy.org.uk/) of circa 2000 children to describe its effects on antibiotic consumption and subsequent consultations in children presenting to primary care with acute respiratory tract infections
4. To use a pragmatic randomised control design to assess the impact of using ScriptSwitch on the use of delayed antibiotic prescribing and subsequent health care consultations.

References:

1. Little P, Rumsby K, Kelly J, et al. Information Leaflet and Antibiotic Prescribing Strategies for Acute Lower Respiratory Tract Infection: A Randomized Controlled Trial. JAMA 2005;**293**(24):3029-35
2. Little P, Gould C, Williamson I, et al. Clinical and psychosocial predictors of illness duration from randomised controlled trial of prescribing strategies for sore throat. British Medical Journal 1999;**319**(7212):736-37
3. Little P, Gould C, Williamson I, et al. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ 2001;**322**(7282):336-42
4. Everitt HA, Little PS, Smith PWF. A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. BMJ 2006;**333**(7563):321
5. Little P, Moore MV, Turner S, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ 2010;**340**(feb05_1):c199

Supervisors: Professor Alastair Hay and Dr Pete Blair (Jon Hayhurst collaborator)

Title: Influence of adolescent alcohol misuse on antisocial behaviour and depressive symptoms in young adulthood

Background:

Early and hazardous drinking in adolescence is associated with adult alcohol consumption and problems,[1,2] as well as with problems during adolescence.[3] It has been argued that during childhood and in adolescence the adverse consequences of drinking alcohol far outweigh the modest number of positive impacts such as social and emotional coping [4]. The UK government recommends that an alcohol-free childhood is the healthiest and best option; and that if children drink alcohol, it should not be until at least the age of 15. Furthermore, it is recommended that 15 to 17 year olds should consume alcohol on no more than one day a week and never exceed recommended adult daily limits Chief Medical Officer, [5]. Young people in the UK report some of the highest rates of alcohol consumption and hazardous drinking in Europe Advisory Council on the Misuse of Drugs, [6,7]. Recent trends suggest that monthly alcohol use may have decreased for young people over 16 and increased for those under 16 but with little change in trends in heavy episodic (binge) drinking and little to no difference between girls and boys with over 50% reporting heavy episodic drinking [7,8]. Average weekly alcohol consumption among women aged 16-19 nearly trebled from ~5 units in 1992 to 14 units per week in 2002 and the gap between men and women has narrowed [9]. Consistent with these data, we recently found that nearly 15% of both boys *and* girls aged 13-15 were classified as "high" frequency drinkers, and that by age 16 over 1 in 3 of boys *and* girls were defined as hazardous drinkers based on reported Alcohol Use Disorders Identification Test (AUDIT) scores [10].

Data:

Repeated self-report measures of alcohol use/misuse from the ALSPAC study along with antisocial behavior and depressive symptoms. To compliment these data there will be the potential to use external information such as criminal behavior through record linkage.

Objectives and Hypotheses:

Through the use of a range of latent variable models the aims will be to:

(1) Examine the potential role of alcohol exposure on the continuation or acceleration of antisococial behavior. Adolescence is a period during which conduct problems / antisocial behaviours will typically diminish. The project will examine and test the hypothesis that: alcohol misuse acts as a *snare* on individual's antisocial behavior preventing "natural maturation".

(2) Examine trends in alcohol misuse and depressive symptoms. Both alcohol and depressive symptoms increase over the adolescent period. The project will test alternative hypotheses that: alcohol exposure boosts depressive symptoms; depressive symptoms boost alcohol exposure; alcohol and depressive symptoms exhibit a bidirectional mutually reinforcing relationship.

References:

1. Hingson RW, Heeren T, Winter MR. Age at Drinking Onset and Alcohol Dependence: Age at Onset, Duration, and Severity. *Arch Pediatr Adolesc Med.* 2006;**160**:739-746.

2. Pitkanen T, Lyyra AL, Pulkkinen L. Age of onset of drinking and the use of alcohol in adulthood: a follow-up study from age 8-42 for females and males. *Addiction.* 2005;**100**:652-661.

3. Fergusson DM, Horwood LJ. Alcohol abuse and crime: a fixed-effects regression analysis. *Addiction.* 2000;**95**:1525-1536.

4. Newbury-Birch D, Gilvarry E, McArdle P, Venkateswaran R, Stewart S, Walker J, et al. *Impact of Alcohol Consumption on Young People: A Systematic Review of Reviews*: DCSF; 2008.
5. CMO. *Draft Guidance on the Consumption of Alcohol by Children and Young People from the Chief Medical Officers of England, Wales and Northern Ireland.*: London: Department of Health; 2009.
6. Malone KM, Waternaux C, Haas GL, Cooper TB, Li S, Mann JJ. Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. *The American journal of psychiatry*. 2003;**160**:773-779.
7. Hibell B, Guttormsson U, Ahlström S, Balakireva O, Bjarnason T, Kokkevi A, et al. *The 2011 ESPAD report. Substance use among students in 36 European countries*: The Swedish Council for Information on Alcohol and Other Drugs, Stockholm, Sweden. ; 2012.
8. Smith LA, Foxcroft DR. *Drinking in the UK: An exploration of trends*: Joseph Rowntree Foundation; York.; 2009.
9. Goddard E. *Estimating alcohol consumption from survey data: updated method of converting volumes to units.* London: ONS HMSO; 2007.
10. Heron J, Macleod J, Munafo MR, Melotti R, Lewis G, Tilling K, et al. Patterns of alcohol use in early adolescence predict problem use at age 16. *Alcohol Alcohol.* 2012;**47**:169-177.

Supervisors: Jon Heron and Matt Hickman

Title: Epigenetic biomarkers of prostate cancer risk

Outline of project:
Epigenetic changes arise early in the pathogenesis of prostate cancer and provide a very promising avenue for the identification and development of biomarkers which can be applied to early detection, diagnosis, staging, risk stratification and treatment monitoring. Numerous alterations to DNA methylation (the most commonly studied form of epigenetic modification) have been documented in studies of prostate tumour tissue. Recent methodological developments open the possibility of the detection of methylation profiles in low levels of circulating tumour DNA in peripheral blood. Furthermore, the exploration of DNA methylation profiles in peripheral blood DNA as early biomarkers of prostate cancer is recognised as a highly promising area. Much of the work published to date has focused on the analysis of tumour biopsy samples and has been limited to a handful of genes (e.g. *GSTP1*, *APC* and *RASSF1a*). A more comprehensive appraisal of epigenetic variation in a large cohort of prospectively collected biological samples pre-dating diagnosis with detailed information on diagnosis, staging, and treatment would greatly enhance progress in this field and assist in addressing the major problems associated with risk stratification in this form of cancer.

Aims:
The aims of the PhD are to:

1. Undertake a case control study (based on 400 cases and 400 controls) of an epigenome-wide analysis of DNA methylation in prostate cancer to identify epigenetic associations with prostate cancer;
2. Apply novel methodological approaches to assess the causality of observed epigenetic associations with prostate cancer; based on triangulating genetic associations of epigenetic changes with their associations with prostate cancer.
3. Utilise a novel methodology – biomarker demendelization – to purge biomarker measures of the genetic contribution to increase the predictive ability of epigenetic changes.
4. Compare methylation in genomic DNA with benign prostate cancer cores to assess how well the methylation of white blood cell DNA correlates with the benign prostate tissue

Proposed Studies:
Matched case-control study nested within the U.K. population–based Prostate testing for cancer and Treatment (ProtecT) study of PSA detected prostate cancer in men aged 50-69 years (400 cases and 400 controls). Between 2001 and 2009, all (approximately 227,300) men aged 50-69 years in 300 general practices located around nine UK cities (centres) were invited to have a PSA test at a prostate check clinic appointment. Participants with a PSA level between 3.0 and 19.9 ng/mL (approximately 10% of men tested) were invited to attend the centre's urology department for digital rectal examination and 10-core trans-rectal ultrasound-guided biopsy. Men with a PSA level $\geq$ 20 ng/mL were referred as a matter of urgency to a urologist, and were eligible to participate in the treatment trial only if localized cancer was confirmed. A diagnosis of localized prostate cancer was defined as a positive biopsy, clinical stage T1-T2, NX, M0; advanced prostate cancer was defined as positive biopsy, clinical stage T3-T4 or N1 or M1. All men provided written informed consent. Trent Multicentre Research Ethics Committee approved the ProtecT study and allied prostate cancer research under the auspices of ProMPT (Prostate Mechanisms of Prostate cancer and Treatment).

The matched cases and controls will be randomly selected and assessed using a recently released genome-wide DNA methylation array (Illumina HumanMethylation450) which

assays 450K CpG sites in the human genome. The assays will be run in the ALSPAC laboratories in the School of Social and Community Medicine, where an existing project (ARIES, http://www.ariesepigenomics.org.uk/) has already established the hardware and informatics to run this array. Causality will be assessed using novel statistical methods described by co-supervisors, Professors Relton and Davey Smith, in the *Int J Epidemiol 2012;41:161–176*. The PhD students will also utilise a novel methodology – biomarker demendelization – to purge biomarker measures of the genetic contribution to increase predictive ability.

In line with current consensus to modelling power requirements in epigenome wide association studies, we propose to follow the models of Balding suggesting that a sample size of 400 case-control pairs provides good power to detect anticipated effect sizes (OR 1.5) (*Nature Rev Genet*, doi:10.1038/nrg3000).

In a collaboration with Professor David Neal we have the potential to access paired genomic DNA and benign prostate cancer cores to assess how well the methylation of white blood cell DNA correlates with the benign prostate tissue. This will provide important insights into the use of non-invasive blood sampling as a marker of tissue-level methylation. Access to tumour tissue will also be possible to investigate any mechanistic links between perturbed methylation profiles in blood and those observed in prostate tumours.

The proposed project is original, multidisciplinary (oncology, epigenetics, epidemiology) and is founded upon exceptional research resources. The consumables cost to undertake this work (approximately £100K) will be supplemented from other secured sources, providing an outstanding opportunity for a productive, data rich studentship.

Industrial partnership will undoubtedly enhance the proposed project and will be particularly pertinent to biomarker development, with the potential for the student to enhance the collaboration over and above biomarker identification.

The student will be trained within a vibrant and varied training environment with supervision from academics with strong research profiles in relevant and complementary fields.
Prostate cancer is the most common cancer in men and the second leading cause of cancer death in the UK. Prostate-specific antigen (PSA) screening has dramatically increased the early diagnosis of prostate cancer because it is highly sensitive. However, the specificity of PSA screening is only 25%, resulting in many unnecessary biopsies and, ultimately, substantial overtreatment. A highly specific circulating biomarker (e.g. using blood samples) that complements the traditional PSA test would therefore be an important advance. A specific and non-invasive test would allow patients to avoid the physical pain and discomfort associated with biopsies and avoid the adverse effects and unnecessary costs resulting from overtreatment. As blood sampling is already essential for PSA screening an additional measurement of whole blood biomarkers would not place any extra burden on patients. Whole genome DNA methylation signatures have the potential to elicit a panel of informative biomarkers with predictive utility.

Supervisors:
Richard Martin, Professor of Clinical Epidemiology with expertise in prostate cancer aetiology and screening, and co-I on the ProtecT trial. Supervised 6 PhD students to completion and currently supervising 5 students. Director of Graduate Studies and lead on Wellcome Trust 4 year PhD programme in Lifecourse, Molecular & Genetic Epidemiology (2008-2013, 18 students).

George Davey Smith, Professor of Clinical Epidemiology with expertise in causal inference, Mendelian randomization and epigenetics. Supervised over 20 PhD students to completion

and currently supervising 5 students. Director of Wellcome Trust 4-year PhD programme in Lifecourse, Molecular & Genetic Epidemiology.

Caroline Relton, Professor of Epigenetic Epidemiology with expertise both of these disciplines. Supervised 2 PhD students to completion and currently supervising 3 students.

Infrastructure is very well established to support PhD students through doctoral studies. The School of Social & Community Medicine attracts high calibre students and has a very high success rate of timely submission and subsequent employment including many fellowships. We have an internationally renowned Short Course Programme (http://www.bris.ac.uk/social-community-medicine/shortcourse), providing unparalleled access to skills training for all our students.

Title: Epigenetic and metabolomic mediators of associations between childhood growth and chronic disease

Background

Patterns of growth in childhood are associated with later chronic disease, but the causality and underlying physiological mechanisms of these associations are poorly understood. Higher BMI – measured in childhood or in adulthood – is associated with greater risk of many diseases, including cancers, cardiovascular diseases, and respiratory diseases. The association between height and chronic disease is more complex, with shorter height showing associations with greater risk of cardiovascular and respiratory diseases, but lower risk of some cancers.

This PhD offers the opportunity to explore these associations and the potential causal mechanisms underlying them, using data from two large prospective studies from Denmark and the UK.

Outline of project

The objectives of this PhD are to:

1) investigate the associations between childhood growth and chronic disease events in adulthood, identifying which features of childhood growth trajectories are related to later chronic disease risk
2) assess the physiological (epigenetic, metabolomic, etc) pathways mediating these relationships
3) establish the causality of these pathways using novel statistical methodologies.

Associations between childhood growth and clinical outcomes will be assessed in a large Danish study, with childhood growth (from school records) and clinical outcomes (from linkage to national registers) available for 372,636 children who attended school in Copenhagen, Denmark from 1936 to 2005.[1 2 3] These relationships could also be assessed in other cohorts with data on both child growth and outcomes in adulthood, e.g. the Christ's Hospital study[4 5], and the Barry Caerphilly Growth Study.[6]

The potential physiological (epigenetic, metabolomic, etc) mediators of these associations will be explored in the Avon Longitudinal Study of Parents and Children[7 8], a prospective birth cohort in which almost 14,000 pregnant women were recruited in the early 1990s. Extensive data are available on child growth[9 10], risk factors for later chronic disease[11 12], and physiological factors that may mediate the relationships between child growth and later chronic disease. All of these traits have been measured at multiple time points, allowing for longitudinal analysis.

In order to establish the causality of the role of epigenetic, metabolomic, and other factors in mediating relationships between child growth and chronic disease, novel statistical methodologies will be used to rule out confounding and reverse causality. For example, the dynamic relationships between changes in growth and changes in epigenetic or metabolomic factors will be assessed using multivariate multilevel models[13], and causality of cross-sectional relationships will be assessed using two-step Mendelian Randomisation.[14]

References

1. Baker JL, Sorensen TI. The Copenhagen School Health Records Register. *Scand J Public Health* 2011;**39**:87-90.
2. Baker JL, Sorensen TI. Obesity research based on the Copenhagen School Health Records Register. *Scand J Public Health* 2011;**39**:196-200.
3. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *New England Journal of Medicine* 2007;**357**:2329-2337.

4. Cole TJ, Cortina-Borja M, Sandhu J, Kelly FP, Pan H. Nonlinear growth generates age changes in the moments of the frequency distribution: the example of height in puberty. *Biostatistics* 2008;**9**:159-171.
5. Sandhu J, Ben-Shlomo Y, Cole TJ, Holly J, Davey Smith G. The impact of childhood body mass index on timing of puberty, adult stature and obesity: a follow-up study based on adolescent anthropometry recorded at Christ's Hospital (1936-1964). *Int J Obes (Lond)* 2006;**30**:14-22.
6. Ben-Shlomo Y, McCarthy A, Hughes R, Tilling K, Davies D, Davey Smith G. Immediate postnatal growth is associated with blood pressure in young adulthood: the Barry Caerphilly Growth Study. *Hypertension* 2008;**52**:638-644.
7. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: The 'Children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2012;
8. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey SG, et al. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2012;
9. Howe LD, Tilling K, Galobardes B, Davey Smith G, Ness AR, Lawlor DA. Socioeconomic disparities in trajectories of adiposity across childhood: findings from a prospective birth cohort. *International Journal of Pediatric Obesity* 2010;**6**:e144-e153.
10. Howe LD, Tilling K, Galobardes B, Davey Smith G, Gunnell D, Lawlor DA. Socioeconomic differences in childhood growth trajectories: at what age do height inequalities emerge? *J Epidemiol Community Health* 2012;**66**:143-148.
11. Howe LD, Tilling K, Benfield L, Logue J, Sattar N, Ness AR, et al. Changes in ponderal index and body mass index across childhood and their associations with fat mass and cardiovascular risk factors at age 15. *PLoS One* 2010;**5**:e15186.
12. Lawlor DA, Benfield L, Logue J, Tilling K, Howe LD, Fraser A, et al. Association between general and central adiposity in childhood, and change in these, with cardiovascular risk factors in adolescence: prospective cohort study. *BMJ* 2010;**341**:c6224.
13. Macdonald-Wallis C, Lawlor DA, Palmer T, Tilling K. Multivariate multilevel spline models for parallel growth processes: application to weight and mean arterial pressure in pregnancy. *Stat Med* 2012;**31**:3147-3164.
14. Relton CL, Davey SG. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. *Int J Epidemiol* 2012;**41**:161-176.

Supervisors: George Davey Smith, Laura Howe with additional external supervision from Professor Thorkild I Sørensen and Dr Jennifer L Baker (Institute of Preventive Medicine, Copenhagen, Denmark)

Title: Can we determine the appropriateness of primary care consultations for children with RTI?

Background: Respiratory tract infections (RTIs) are cost the NHS and UK society many £100Ms per annum. Around 25% of people with RTIs choose to consult the NHS, most frequently for the very young and the elderly. The choice to consult is more complex for parents making decisions on behalf of their children. However, little is known regarding the appropriateness of these consultations – and from whose perspective – the parent, the consulting clinician and the NHS provider.
A brief search (28 November 2013) of the Medline and Embase databases using terms {'primary care' or ambulatory care} and {appropriateness} and {consultations] identified only 60 studies, most of which were not relevant.

Aim: To conduct a series of mixed method studies to establish if a clinical 'appropriateness tool' can be developed and tested in the context of parental medical help seeking behaviour for children with common RTIs.

Objectives:

1. To conduct a systematic review of the literature for an existing appropriateness measure and, assuming none already exists, to establish the likely components of such a tool from other illness and disease areas, including those that have used UCLA RAND[1] methodology.
2. If insufficient existing literature, to use qualitative methods with parent-clinician pairs to understand perceptions of consultation appropriateness
3. To develop and validate a childhood RTI consultation appropriateness tool from the clinician's perspective
4. To quantify the proportion of children's consultations regarded by clinicians as appropriate

References:

1. Fitch K, Bernstein SJ, Aguilar MD. *The RAND/UCLA Appropriateness Methods User's Manual*. Santa Monica: RAND, 2001.

Supervisors:
Alastair Hay & Patricia Lucas

Title: Life course area deprivation and the risk of asthma and atopy phenotypes in childhood and early adolescence

Background

Socioeconomic inequalities in health persist despite efforts to tackle them. The role and mechanisms through which socioeconomic factors at individual and area ('contextual') level are embodied resulting in ill health requires elucidation. Across a range of outcomes, associations between area deprivation, a composite measure of the local economic, social and physical environment, and health have been reported; these have been robust to adjustment by individual-level socioeconomic position (e.g. education, occupational class, household income). However, the evidence comes primarily from cross-sectional studies, or longitudinal studies with single time-point measures of exposure and outcome, and with limited individual-level measures and relatively course deprivation indices. Detailed life course assessment of exposures that mediate the pathways between socioeconomic exposures and respiratory health, in particular asthma and atopy-related phenotypes, is limited.

Objectives

A systematic literature review of the current evidence for an association of area deprivation with respiratory and atopy outcomes.

1) Determine whether there is an independent (of individual socioeconomic characteristics) association between early life area deprivation and lung function, doctor diagnosis of asthma and atopy phenotypes in children at ages 7-9 and 15-17 years.

2) Determine whether specific area deprivation domains relate to later respiratory and atopy phenotypes.

3) Determine individual level life course exposures that may mediate the associations reported in objectives 1 and 2.

Methods

Study participants: ALSPAC is a prospective birth cohort that recruited 14,541 pregnant women resident in the county of Avon with an expected date of delivery between 1st April 1991 and 31st December 1992, and followed them and their offspring from the time of the pregnancy to age 15-17 for this project (http://www.bristol.ac.uk/alspac). The study catchment area has a population of 1 million and includes the city of Bristol (0.5 million) with a mixture of rural areas, inner city deprivation, affluent suburbs and moderate sized towns. The cohort of ALSPAC has been extensively phenotyped and there is a detailed characterization of risk factors and exposures through medical and other administrative records, questionnaires and clinic visits carried out from pregnancy: 4 maternal and 2 partner's questionnaires during pregnancy; 17 mother-based, 15 partner-based and 23 child-based questionnaires during childhood; with children starting to respond to questionnaires from the age of 7y. Since aged 7y children have been invited to biannual clinical assessments.

Outcome variables, Assessment of asthma phenotypes and lung function: 1) Lung function obtained through spirometry at ages 8-9y and 15-17y (FVC, FEV_1, FEF_{25-75}); 2) asthma (doctor's diagnosis of asthma at ages 8y and 15y); 3) atopy (Skin Prick test at age 7y and 15y); and, 3) combined asthma and atopy phenotypes which classify children into No asthma and no atopy (reference group), asthma alone, asthma with atopy and atopy alone. Secondary outcomes will include: wheezing phenotypes from birth until age 7 years and extended to 15 years which classify children based on their patterns of wheezing over time, bronchial reactivity measured with methacoline challenge at age 8y and fractional exhaled nitric oxide (FeNO) concentrations to asses airway inflammation at age 15y.

Exposure variables, individual and area socioeconomic position (SEP): Several indicators will capture multiple aspects of this construct.

Individual-level SEP: 1) *education* (maternal and paternal); 2) *occupational class* (maternal and paternal); 3) *household income*; 4) *housing tenure;* and 5) *car access*. These were measured at pregnancy, ages 7-8y and 18y. We will analyze each specific indicator separately to evaluate distinct pathways, and also as a composite SEP index obtained with factor analysis.

Area-level SEP/deprivation and area attributes: 1) *Townsend index* (includes unemployment, overcrowding, car access and home ownership) derived from 1990 census data at ward level (will index area deprivation at pregnancy); 2) *Index of multiple deprivation (IMD*2004 and IMD2010) at the Lower Layer Super Output Area which has a minimum population of 1000 and a mean population of 1500 (these correspond approximately to ages 8y and 16y in our sample).

Statistical analysis:

Initial descriptive analysis of area deprivation and health outcomes

Multivariate statistical techniques will include linear regression models for linear health outcomes (e.g. lung function), logistic regression analysis (e.g. doctor's diagnosis of asthma)

Multilevel regression analysis will be used to establish whether an association between area deprivation and outcomes is independent of individual level characteristics.

We will test different models of life course exposure to deprivation (accumulation, critical period and effect modification) by comparing each model specification to an all-inclusive saturated model as described in Mishra et al.[41] These models will evaluate the role of these different life course patterns of deprivation (independent variable) with asthma phenotypes/lung function and with DNA methylation (dependent variables).

Missing data. Multiple imputation using the extensive data available from baseline and the first years of life in ALSPAC will be used in sensitivity analyses to examine the likelihood of selection bias due to loss to follow-up / missing data. We will also use sensitivity analyses to examine the robustness of the results under the assumption that outcome data are missing not at random[42].

References: Krieger N. Epidemiology and the people's health. First ed. Cary: Oxford University Press, 2011.

Macintyre S, Ellaway A, Cummins S. Place effects on health: how can we conceptualise, operationalise and measure them? *Soc Sci Med* 2002;55:125-39.
Hafkamp-de GE, van RL, de Jongste JC, et al.The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschoolasthma symptoms: the Generation R Study. *J Epidemiol Community Health* 2012;66: 1017-24.
Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med* 2012;17:82-91.
Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.
Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63:974-80.
Braback L, Hjern A, Rasmussen F.Social class in asthma and allergic rhinitis: a national cohort study over three decades. *Eur Respir J* 2005;26: 1064-8.
Juhn YJ, Qin R, Urm S, Katusic S, Vargas-Chanes D. The influence of neighborhood environment on the incidence of childhood asthma: A propensity score approach. *J Allergy Clin Immunol* 2010;125:838-43.
Boyd A, Golding J, Macleod J, et al.Cohort Profile: The 'Children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children.*Int J Epidemiol* 2012;
Mishra G, Nitsch D, Black S, et al. A structured approach to modelling the effects of binary exposure variables over the life course. *Int J Epidemiol* 2009;38:528-37.

Supervisor(s): Bruna Galobardes (bruna.galobardes@bristol.ac.uk). Additional supervisors (Prof Tilling and Prof Henderson) will be available.

Title: Maternal haemoglobin in pregnancy: trajectories, risk factors and consequences for offspring. The Avon Longitudinal Study of Parents and Children (ALSPAC)

Background:

Maternal haemoglobin concentrations are known to decrease in early pregnancy, with a slight increase towards the end of gestation.(1) Women who have haemoglobin concentrations at either the bottom (maternal anaemia) or the top end of the distribution in each trimester have been found to have a higher risk of delivering a low birth weight offspring and delivering preterm compared with those with mid-range haemoglobin levels.(2-3) However, a greater decrease in haemoglobin between trimesters is associated with a reduced risk of preterm birth.(4) Risk factors such as older maternal age, being overweight pre-pregnancy, lower maternal education, multiparity and twin pregnancy have been reported to be associated with maternal anaemia (low haemoglobin) during pregnancy,(5) but it is not clear whether these are also associated with the pattern of change in haemoglobin across pregnancy.

Iron is essential for proper cell differentiation and cell growth and plays an important role in the functioning of the immune system(6) Whilst it has generally been assumed that infants born at term and with an adequate birth weight have adequate iron stores for the first 4–6 months of life, several studies(e.g. 7,8) have shown an association between maternal pregnancy haemoglobin concentrations and iron status in offspring in infancy. Hence it is possible that maternal haemoglobin concentrations are associated with offspring outcomes both in infancy and later on in life.

Objectives

1. To describe the average pattern of change in haemoglobin concentrations during pregnancy.
2. To examine associations of potential risk factors with maternal haemoglobin concentrations and/or patterns of changes in haemoglobin across the course of pregnancy.
3. To investigate the associations of maternal haemoglobin concentrations and/or patterns of changes in haemoglobin during pregnancy with the following outcomes in offspring:
    a. patterns of growth in childhood and adolescence
    b. childhood infections
    c. cardiovascular risk factors (e.g. blood pressure, lipids, insulin, glucose) during childhood and adolescence
    d. cognitive and behavioural outcomes in childhood and adolescence
    e. respiratory health in childhood and adolescence
4. To assess whether there is a causal relationship between maternal haemoglobin concentrations in pregnancy and offspring outcomes using a Mendelian randomization approach.
5. To determine whether differential methylation patterns in offspring cord blood mediate any of the observed associations.

The Avon Longitudinal Study of Parents and Children (ALSPAC)

ALSPAC is a longitudinal, population-based pregnancy cohort based in Bristol that recruited 14,541 pregnancies with expected dates of delivery 1st April 1991 to 31st December 1992 (http://www.alspac.bris.ac.uk.)(9)

In ALSPAC all antenatal haemoglobin measurements have been abstracted from obstetric records (median 3 and interquartile range of 2 to 3 measurements per woman). Early and late pregnancy haemoglobin concentrations have been derived from these routinely collected measurements and it is possible to longitudinally model trajectories of change in haemoglobin

across pregnancy using multilevel models. In addition, there is genome wide data on both mothers and offspring and DNA methylation is available for a subgroup.

There are a number of potential PhD projects that could be undertaken based on this proposal, from the very statistical to the much more applied. The student will be encouraged to develop a work plan based around their interests. Students may choose to combine a classic epidemiologic approach with a focus on one or more of statistical modeling of repeat measures (in Stata and/or MLwiN) using multilevel models, strengthening causal inference using a Mendelian randomization approach, investigating the role of epigenetics in explaining observed associations.

References:

1. Meng Lu ZG, RL; Cliver, SP; Cutter, G, Blankson M. The relationship between maternal hematocrit and pregnancy outcome. Obs & Gynecol. 1991;77(2):190-4.
2. Steer P, Alam MA, Wadsworth J, Welch A. Relation between Maternal Hemoglobin Concentration and Birth-Weight in Different Ethnic-Groups. BMJ. 1995;310(6978):489-91.
3. Zhou LM, Yang WW, Hua JZ, Deng CQ, Tao XG, Stoltzfus RJ. Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. Am J Epidemiol. 1998;148(10):998-1006.
4. Zhang QY, Ananth CV, Li Z, Smulian JC. Maternal anaemia and preterm birth: a prospective cohort study. Int J Epidemiol. 2009;38(5):1380-9.
5. Zhang QY, Li Z, Ananth CV. Prevalence and risk factors for anaemia in pregnant women: a population-based prospective cohort study in China. Paediatric and Perinatal Epidemiol. 2009;23(4):282-91.
6. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S-579S.
7. de Pee S, Bloem MW, Sari M, Kiess L, Yip R, Kosen S. The High Prevalence of Low Hemoglobin Concentration among Indonesian Infants Aged 3-5 Months Is Related to Maternal Anemia. *J Nutr* 2002;132:2215-2221.
8. Chaparro CM. Setting the stage for child health and development: prevention of iron deficiency in early infancy. *J Nutr* 2008;138:2529-2533.
9. Fraser A, MacDonal-Wallis C, Tilling K, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol. 2013;42:97-110.

Supervisor(s): Please contact Abigail Fraser (Abigail.Fraser@bristol.ac.uk) in the first instance.

Title: Childhood abuse and intimate partner violence and their long term health sequelae: the Avon Longitudinal Study of Parents and Children

Background

In recent years, the potential role of abuse victimization in both childhood and adulthood in the aetiology of obesity and cardiovascular diseases has attracted increasing interest. This reflects the growing recognition of the role of psychosocial risk factors in cardiovascular risk[1], as well as the co-occurrence of mental and cardiovascular ill-health[2]. Long term health sequelae of childhood abuse are severe and numerous and include depression, anxiety, eating disorders, illicit drug use, alcohol abuse, and risky sexual behaviour. An emerging body of evidence suggests that a history of child abuse is also associated with growth trajectories[3], greater adiposity[4,5], food addiction[6], hypertension[7], diabetes mellitus[8], smoking[9,10], inflammation markers[11], and cardiovascular disease (CVD) events in later life[12-17]. Less is known about the associations of both childhood abuse and IPV with cardiometabolic and mental health in men, though some studies of child abuse have included both men and women[13,15,16], with one study reporting an association of childhood sexual abuse with an increased risk of myocardial infarction in men but not in women[18]. In women, associations of IPV with smoking, high cholesterol, heart disease and stroke have also been found and these were stronger than equivalent associations in men[19]. Interestingly, in the US Nurses Health II Study, physical and sexual IPV in adulthood were not strongly associated with an increased risk of hypertension[20] or diabetes[21], though severe psychological abuse (indicated by only 2% of cohort members) was associated with both.

Evidence in support of a role of abuse in the aetiology of cardiometabolic ill-health stems from several sources. Preclinical and clinical studies demonstrate profound and lasting effects of early stress on the hypothalamic-pituitary-adrenal and noradrenergic stress systems, including heightened glucocorticoid, norepinephrine, and autonomic stress reactivity, as well as altered dopaminergic and serotonergic function[22-25]. Survivors of childhood sexual abuse have increased heart rate and blood pressure response to cognitive and social challenges[26]. Moreover, posttraumatic stress disorder is prevalent among abused women[27] and is associated with increased risks of coronary heart disease, smoking[9], overweight[28], dyslipidemia[29], diabetes mellitus[30], hypertension[31], and possibly inflammation[32]. Finally, epigenetic processes affecting gene expression may be mediators of these postulated pathways[33].

The Avon Longitudinal Study of Parents and Children (ALSPAC) offers a unique opportunity to study patterns of experience and perpetration of abuse across the lifecourse and their association with cardiometabolic health in both men and women, and potentially across two generations in the same family.

Aims:

The following are potential aims for this project and not all have to be addressed.
The student will be encouraged to develop a work plan based around their own interests, results of a literature review (see aim 1) and the data available in ALSPAC and other cohorts.

1. To systematically review the evidence on the association between child and adult abuse with cardiometabolic health and other outcomes of interest.
2. To estimate the concordance between different family members' (mothers, fathers and offspring trios) responses to questions regarding abuse taking into account different time points and wording of the questions
3. To study associations of childhood abuse with cardiometabolic and other outcomes of interest.

4. To describe longitudinal trajectories of IPV and assess their association with cardiometabolic and other outcomes of interest.
5. To investigate the co-occurrence of abuse in childhood and IPV in adulthood and to investigate whether IPV modifies associations of abuse in childhood with cardiometabolic health and other outcomes of interest.
6. To investigate the role of established cardiometabolic risk factors (adiposity, smoking, alcohol intake) in explaining associations between abuse and cardiometabolic health.
7. To investigate the role of mental health in explaining associations of interest.
8. To investigate the potential role of differential DNA methylation in associations of interest.

Data:
The Avon Longitudinal Study of Parent and Children (http://www.bristol.ac.uk/alspac/) is a prospective birth cohort with over 20 years of active follow up of both parents and their offspring[34,35]. Participants have been asked about effects of parental emotional and physical cruelty in childhood, sexual abuse in childhood, and IPV, the latter on more than one occasion. Detailed information is available on socio-economic indicators, mental health, health related behaviours (e.g smoking, alcohol intake, drug use), and various other potential sources of stress such as financial difficulties. Adiposity (BMI and DXA assessed fat mass) and measures of cardiometabolic health (e.g. blood pressure, lipids, glucose, insulin, inflammation markers, measures of cardiac structure and function (offspring), carotid intima media thickness (mums and offspring) and pulse wave velocity (fathers) have also been repeatedly assessed.

Reference List

1. Neylon A, Canniffe C, Anand S, Kreatsoulas C, Blake GJ, et al. (2013) A global perspective on psychosocial risk factors for cardiovascular disease. Prog Cardiovasc Dis 55: 574-581.
2. Elderon L, Whooley MA (2013) Depression and Cardiovascular Disease. Progress in Cardiovascular Diseases 55: 511-523.
3. Denholm R, Power C, Li L (2013) Adverse childhood experiences and child-to-adult height trajectories in the 1958 British birth cohort. International Journal of Epidemiology 42: 1399-1409.
4. Noll JG, Zeller MH, Trickett PK, Putnam FW (2007) Obesity risk for female victims of childhood sexual abuse: a prospective study. Pediatrics 120: e61-67.
5. Williamson DF, Thompson TJ, Anda RF, Dietz WH, Felitti V (2002) Body weight and obesity in adults and self-reported abuse in childhood. Int J Obes Relat Metab Disord 26: 1075-1082.
6. Mason SM, Flint AJ, Field AE, Austin SB, Rich-Edwards JW (2013) Abuse victimization in childhood or adolescence and risk of food addiction in adult women. Obesity (Silver Spring).
7. Riley EH, Wright RJ, Jun HJ, Hibert EN, Rich-Edwards JW (2010) Hypertension in adult survivors of child abuse: observations from the Nurses' Health Study II. J Epidemiol Community Health 64: 413-418.
8. Rich-Edwards JW, Spiegelman D, Lividoti Hibert EN, Jun HJ, Todd TJ, et al. (2010) Abuse in childhood and adolescence as a predictor of type 2 diabetes in adult women. Am J Prev Med 39: 529-536.
9. Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, et al. (1999) Adverse childhood experiences and smoking during adolescence and adulthood. JAMA 282: 1652-1658.
10. Nichols HB, Harlow BL (2004) Childhood abuse and risk of smoking onset. J Epidemiol Community Health 58: 402-406.

11. Bertone-Johnson ER, Whitcomb BW, Missmer SA, Karlson EW, Rich-Edwards JW (2012) Inflammation and early-life abuse in women. Am J Prev Med 43: 611-620.
12. Rich-Edwards JW, Mason S, Rexrode K, Spiegelman D, Hibert E, et al. (2012) Physical and sexual abuse in childhood as predictors of early-onset cardiovascular events in women. Circulation 126: 920-927.
13. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, et al. (2004) Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation 110: 1761-1766.
14. Goodwin RD, Stein MB (2004) Association between childhood trauma and physical disorders among adults in the United States. Psychol Med 34: 509-520.
15. Scott KM, Von Korff M, Angermeyer MC, Benjet C, Bruffaerts R, et al. (2011) Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. Arch Gen Psychiatry 68: 838-844.
16. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, et al. (1998) Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14: 245-258.
17. Batten SV, Aslan M, Maciejewski PK, Mazure CM (2004) Childhood maltreatment as a risk factor for adult cardiovascular disease and depression. J Clin Psychiatry 65: 249-254.
18. Fuller-Thomson E, Bejan R, Hunter JT, Grundland T, Brennenstuhl S (2012) The link between childhood sexual abuse and myocardial infarction in a population-based study. Child Abuse Negl 36: 656-665.
19. Breiding MJ, Black MC, Ryan GW (2008) Chronic Disease and Health Risk Behaviors Associated with Intimate Partner Violence—18 U.S. States/Territories, 2005. Annals of Epidemiology 18: 538-544.
20. Mason SM, Wright RJ, Hibert EN, Spiegelman D, Forman JP, et al. (2012) Intimate partner violence and incidence of hypertension in women. Ann Epidemiol 22: 562-567.
21. Mason SM, Wright RJ, Hibert EN, Spiegelman D, Jun HJ, et al. (2013) Intimate partner violence and incidence of type 2 diabetes in women. Diabetes Care 36: 1159-1165.
22. Bremner JD, Vermetten E (2001) Stress and development: behavioral and biological consequences. Dev Psychopathol 13: 473-489.
23. Bremner JD, Vythilingam M, Vermetten E, Adil J, Khan S, et al. (2003) Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse. Psychoneuroendocrinology 28: 733-750.
24. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, et al. (2003) The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 27: 33-44.
25. Kaufman J, Charney D (2001) Effects of early stress on brain structure and function: implications for understanding the relationship between child maltreatment and depression. Dev Psychopathol 13: 451-471.
26. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, et al. (2000) Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 284: 592-597.
27. Woods SJ, Campbell JC (1993) Posttraumatic stress in battered women: does the diagnosis fit? Issues Ment Health Nurs 14: 173-186.
28. Dobie DJ, Kivlahan DR, Maynard C, Bush KR, Davis TM, et al. (2004) Posttraumatic stress disorder in female veterans: association with self-reported health problems and functional impairment. Arch Intern Med 164: 394-400.
29. Kagan BL, Leskin G, Haas B, Wilkins J, Foy D (1999) Elevated lipid levels in Vietnam veterans with chronic posttraumatic stress disorder. Biol Psychiatry 45: 374-377.
30. Goodwin RD, Davidson JR (2005) Self-reported diabetes and posttraumatic stress disorder among adults in the community. Prev Med 40: 570-574.

31. Buckley TC, Kaloupek DG (2001) A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. Psychosom Med 63: 585-594.
32. von Kanel R, Hepp U, Kraemer B, Traber R, Keel M, et al. (2007) Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res 41: 744-752.
33. McGowan PO (2013) Epigenomic Mechanisms of Early Adversity and HPA Dysfunction: Considerations for PTSD Research. Front Psychiatry 4: 110.
34. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, et al. (2012) Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. International Journal of Epidemiology.
35. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, et al. (2012) Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International Journal of Epidemiology.

Potential supervisors:
Dr. Abigail Fraser, Dr. Laura Howe, Prof. Gene Feder

Title: Age at puberty and cardiometabolic health in adolescence

Background

Cardiovascular diseases (CVD) are the leading cause of death worldwide. Whilst the vast majority of cardiovascular events occur from middle age onwards, cardiovascular risk is known to start in early life. Early puberty has been postulated as a risk factor for CVD; studies have demonstrated associations between earlier puberty and greater CVD risk. However, the causality of these associations is not established. This proposal explores the association between age at puberty and cardiometabolic health in late adolescence, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) primarily.
This project is an opportunity to work on a longitudinal study with repeat measures. Below are a number of potential objectives that could be the basis for more than one distinct PhD. We would anticipate students studying in depth 2-3 of the objectives and adding their own areas of interest in relation to the broad topic of age at puberty and cardiometabolic health later in life. Students may choose to focus on statistical methodology (modelling repeat measures, causal inference), on the more applied objectives, or a mixture of the two.

Objectives

1. To examine associations of age at puberty (age at menarche in females and peak height velocity in females and males) with atherosclerosis (carotid intima media thickness) and measures of cardiac structure and function (from conventional and tissue Doppler echocardiography) at age 17 years.
2. To examine associations of age at puberty with trajectories (changes over time) of blood pressure, lipids, glucose and insulin in adolescence using repeated measures of blood pressure, lipids, glucose and insulin throughout adolescence.

To examine potential pathways linking age at puberty and cardiometabolic health:

3. To assess whether i. declines in physical activity, greater likelihood of smoking initiation, and/or ii. greater subsequent increases in adiposity (measured by BMI, whole-body and central fat mass from age at puberty to age 17) mediate any association between age at puberty and cardiovascular structure and function at age 17.
4. To use a Mendelian Randomization approach and/or a sibling study design to improve causal inference regarding the relationship between age at puberty and cardiometabolic health later in life.

Supervisors/Collaborators

Dr Laura Howe and Dr Abigail Fraser (Supervisors)

Title: How strong is the evidence that interventions intended to reduce unplanned conception in adolescent girls have influenced recent rates in teenage pregnancy in England: review of reviews and analysis of routine data

Background:

In the last decade there have been several major shifts in sexual health policy aimed at reducing unplanned pregnancy, and especially in adolescent girls aged <18. This is reflected in two policies in the Sexual Health Outcomes Framework

1) to reduce unwanted pregnancies by ensuring that people have access to the full range of contraception, can obtain their chosen method quickly and easily and can take control to plan the number of and spacing between their children
2) to support women with unwanted pregnancies to make informed decisions about their options as early as possible. [1]

Evidence for the effectiveness of interventions intended to reduce unplanned conception amongst adolescent girls is mixed. A systematic review by DiCenso and colleagues (BMJ 2002, [2]) found no evidence for effectiveness of interventions intended to delay sexual debut, increase contraceptive use or reduce unplanned conception. A later review by Harden and colleagues (BMJ 2009, [3]) reported some evidence of effectiveness of early childhood interventions and youth development programmes in reducing unintended pregnancy. Intervention policy in this area is often based on face validity and pragmatism as much as strong unbiased evidence for effectiveness. Thus elements of current policy in England typically include increasing availability of long-acting reversible contraception (LARC), especially to younger pre-partum women, over the counter availability of emergency hormonal contraception (EHC) and other intensive interventions with young women following termination of pregnancy (TOP) or unplanned teenage pregnancy. Rates of teenage pregnancy are typically higher in more disadvantaged social groups. One concern is that effective interventions to reduce unplanned conceptions may increase this health inequality if they are accessed more effectively by young women who are relatively socially advantaged.

Aims:

This project aims to collate and analyse routinely collected data at local authority ward data to assess the changes in teenage pregnancy and other associated outcomes to determine trends in different socio-economic groups. The pathway to unplanned pregnancy is complex, involving multiple interventions, making analysis of the impact of individual components challenging. We will build a model of interventions to prevent unplanned pregnancy and integrate this with data on outcomes and service delivery (including EHC, LARC, condom use, teenage unplanned pregnancy, repeat TOP, late TOP and STIs). We will include details of service provision and burden in the Bristol area (Bristol, South Gloucestershire and North Somerset) and compare this against the national picture. We will use data from NATSAL-3 and ALSPAC (Avon Longitudinal Study of Parents and Children) to inform and contextualise the findings through understanding sexual behaviour and risk profile of young people.

This project will involve data manipulation and statistical analysis. A review of reviews on the effectiveness of interventions intended to reduce unintended teenage pregnancy will be undertaken and updated with further literature searches as appropriate. The candidate will work closely with Bristol Health Partners and the Sexual Health Improvement Programme (SHIPP) teams.

Epidemiology and Health Service Research

References

1) A Framework for Sexual Health Improvement in England. DH and cross Government. 15 March 2013 Ref: 18420

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/142592/9287-2900714-TSO-SexualHealthPolicyNW_ACCESSIBLE.pdf

2) DiCenso, A., G. Guyatt, A. Willan and L. Griffith (2002). "Interventions to reduce unintended pregnancies among adolescents: systematic review of randomised controlled trials." BMJ **324**(7351): 1426.
3) Harden, A., G. Brunton, A. Fletcher and A. Oakley (2009). "Teenage pregnancy and social disadvantage: systematic review integrating controlled trials and qualitative studies." BMJ **339**: b4254.

Supervisors/Collaborators
Prof John Macleod & Dr Katy Turner

Title: Improving the design of pilot work to inform main RCTs in surgery

Background:
The MRC guidance for evaluating complex interventions recommends pilot work is undertaken before a main trial[1]. It has recently been recognised that invasive clinical interventions, such as surgery, are complex because of multiple interacting components and because intervention outcomes are dependent upon operator and team expertise[2]. Whilst pilot work to inform a main trial design often focuses on recruitment targets, treatment effect size to inform the magnitude of the main trial and safety and toxicity issues, there are many other opportunities within pilot work to optimise a main trial. and these issues are pertinent in trials of complex interventions[3-5]. Methodological issues that may be addressed include, complexity/adherence to the intervention, blinding of outcome assessors and other staff, logistics of the trial being applied in different teams and clinical centres and retention. For surgical trials pilot studies also provide the opportunity for interventions to educate recruiters in trial methodology and recruitment because of the lack of evidence based culture in this field. Methods to utilise pilot work to optimise trial design for RCTs in surgery and other invasive procedures are currently lacking and this area has hitherto not been explored or established. The overall aim of this PhD, therefore, is to explore how pilot work has optimally informed trial design of surgical interventions and to consider new methods to improve this.

Research question:
How can pilot work for trials of surgical procedures be optimised to improve the main trial design?

Objectives and methods:
i) To undertake a literature review of all types of pilot work in RCTs in surgery to identify and summarise current practice including analyses of the NIHR database of trial protocols to review key features in the design of internal and external pilot studies and their association with successful progression trials in surgery, ii) To use qualitative research methods to explore perceptions of surgeons (CIs) and triallists of when to undertake pilot work in a surgical RCT focussing upon intervention standardisation and innovation and to, iii) To use consensus methods to bring together surgeons and methodologists to consider evidence and practice and to make recommendations for optimal design of pilot work in trials in surgery.

The student would be a member of the ConDuCT Hub for Trials Methodology Research.

References:
1) A framework for the development and evaluation of RCTs /or complex interventions to improve health. London: MRC, 2000.
2) Ergina P, Cook J, Blazeby J, et al Challenges in evaluating surgical innovation. Lancet 2009;374(9695):1097-104.
3) Shanyinde M, et al. Questions asked and answered in pilot and feasibility randomized controlled trials. BMC Med Res Methodol. 2011;11:117.
4) Lancaster G, Dodd S, Williamson P. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004;10(2):307-12,
5) Arain M, Campbell M, Cooper C, Lancaster G. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol. 2010;10:67.

Supervisors/Collaborators: The North West Hub for Trial Methodology Research (via Williamson) and Royal College of Surgeons of England Surgical Trials Centres

Title: Powering trials on effectiveness and efficacy outcomes

Background:

Currently trials are powered on a single, clinical efficacy end-point, and yet decisions on whether to adopt a new treatment are based on broader assessments of its impact on patients lives. NICE, for example, uses measures of life-time QALY impact. Because measures such as the EQ-5D are usually considerably less sensitive to treatment effects than disease specific measures used as trial end-points, trials are almost invariably under-powered to detect QALY effects. As a result, the practice has developed of "mapping" treatment effects from disease-specific measures into QALYs, using an externally derived mapping coefficient. This practice assumes there is a functional relation between the disease-specific and QALY scales.

Objectives:

The purpose of the PhD project is to develop new ways of powering trials on multiple outcomes, where the outcomes are functionally related. This will lead, potentially, to *smaller* trials providing *more* information on economically significant outcomes such as QALYs.

Methods:

The PhD research will include a review of current approaches to the role of economic outcomes in powering trials, and current practices among manufacturers in choosing whether to power on efficacy or on economic outcomes. The core work will involve mathematical analysis of how trial size (power) depends on the: relative responsiveness of different test instruments to treatment differences; uncertainty in the mappings; correlations between responses to test instruments; and the functional relationships between treatment effects on different test instruments. The methods will be applied in fully work-up examples, where the sample sizes required to reach a given power under standard and multiple outcomes with mapping methods, will be contrasted. The work will take as a starting point the work of Ades and Lu (2013), and will develop this further to consider multiple disease-specific and/or Quality of Life outcomes. Value of Information methods will be developed to determine whether it is efficient to collect further information on mappings prior to trial design.

Reference:

Ades AE,Lu G,Madan JJ. Which Health-Related Quality-of-Life Outcome When Planning Randomized Trials: Disease-Specific or Generic, or Both? A Common Factor Model. Value in Health 2013:185-194.

Supervisors/Collaborators:

The student would be a member of the ConDuCT Hub for Trials Methodology Research.

35

Title: Optimising the design and conduct of screening logs within pragmatic trials to understand and improve recruitment

Background:
Systematic reviews of methods to optimise trial recruitment highlight the need for a better understanding of the recruitment process[1]. The recruitment process is started when potentially eligible participants are screened for eligibility and it continues when eligible participants are offered randomisation. Understanding the numbers and reasons for not screening participants, for participants not being eligible for trials and for some not consenting to randomisation, provides critical information that can be used to manage and optimise recruitment. In addition, for pragmatic trials, understanding how centres and staff apply eligibility criteria provides information about the generalizability of the trial. Whilst these issues may be acknowledged and data may theoretically be collected in some trials in both screening, and, pre-screening logs, there is evidence that few published trials report this information accurately and good examples are uncommon[2]. In particular, the reasons for not screening potentially eligible participants and for how eligibility criteria may be applied variably between centres (thus making recruitment rates different between centres)need investigation. Previous work in the ConDuCT Hub has explored these issues but methods for obtaining the data and ethical considerations around these issues are not well developed or established and many teams recruiting patients do not use these approaches, focusing on reporting recruitment figures. The overall aim of this PhD project therefore is to further understand the recruitment process in trials and to develop optimal methods for designing and using screening logs.

Question: How can screening logs be designed and used to optimise trial recruitment?

Objectives: i) To review current practice regarding the use of screening logs to inform trial recruitment, ii) Develop methods for the optimal design and use of logs including developing templates to use for ethical committee applications

Methods: Mixed methods will be used to collate and analyse screening logs and to interview staff about logs, rationale for use and completion of the data. The study may focus on a particular clinical area (e.g. trials in surgery) depending on the candidate. Semi-structured interviews will explore triallists' and recruiting staffs' views to understand their use/lack of use of screening logs at all stages through the recruitment process. Exemplar practice will be identified and used to inform the second part of the study. The second part of the project will develop and pilot screening logs and examine how they are sued in practice. In addition the study will develop a framework to use in ethics committee application to apply to the collection of anonymised data in screening logs.

The student would be a member of the ConDuCT Hub for Trials Methodology Research.

References:
1) Treweek S *et al*. Methods to improve recruitment to RCTs: Cochrane systematic review. *BMJ Open* 2013;3(2).
2) http://www.consort-statement.org/consort-library/13-19-results/13a---participant-flow/.

Supervisors/Collaborators:
CTUs via collaborations with Profs K Hood, A Montgomery, J Bliss, B Reeves, P Williamson, and, Drs G Griffiths, C Rogers, A Lane, C Metcalfe.

36

Title: Synthesis and Value of Information for trial design with surrogate outcomes

Background:

Surrogate outcomes are increasingly being used in RCTs to assess efficacy of health technologies. Surrogate outcomes are attractive in RCTs because they can be measured more cheaply/easily than the primary clinical outcome of interest, due to (i) shorter-term follow-up and lower numbers of patients being required to achieve a desired power to detect differences between health technologies, and/or (ii) reduced resource use required to perform the measurement. Ideally, a 'valid' surrogate will perfectly predict the primary clinical endpoint of interest. However, in practice surrogate validity is a matter of degree. The information provided by, and hence the value of, RCTs reporting surrogate outcomes will depend on the strength and nature of the relationship between the surrogate and primary outcomes. A question faced by trial designers and research funders is therefore whether it is sufficient to run a trial with a surrogate outcome, or whether it is worth the extra resources to measure the primary outcome of interest. Value of Information (VOI) measures the anticipated net benefit gained from running a new study with a specific design, to add to the evidence on which reimbursement decisions are made. Whilst the primary clinical endpoint is what is required to inform a cost-effectiveness analysis (CEA), surrogates may also provide information if they predict the primary outcome well. Methods for synthesis of both surrogate and primary outcomes have been proposed, but to date they have not been used in practice to inform CEA, VOI, and trial design.

The aim of this PhD is to develop methodology for the synthesis of studies reporting surrogate and/or primary clinical outcomes, and VOI methods to inform the design of future RCTs. This will enable us to address the following questions: (i) Is there a need for further research to inform efficacy and/or side-effects? (ii) What is the relative value of a trial measuring surrogate, primary, or both outcomes? (iii) What is the optimal sample size for trials with these outcomes? The methods will help identify the balance between benefits to patients by making a treatment available sooner *vs* the costs of the additional uncertainty introduced by use of surrogates. The methods will be illustrated using an example of statins for the treatment of hypercholesterolaemia, and extended to include the consideration of newer drugs in a different class (e.g. ezetimibe). The PhD will explore under which circumstances in general it may be worth collecting primary rather than surrogate outcomes. The student would be a member of the ConDuCT Hub for Trials Methodology Research.

Supervisors/Collaborators:

Dr. Nicky J Welton, Dr. Sofia Dias, Prof. AE Ades

Title: Do antibiotics reduce risk of complications in children with respiratory tract infections?

Background:
Antibiotics are commonly prescribed by GPs and nurses for children presenting to primary care with respiratory tract infections (RTIs). One of the main reasons for prescribing is to avoid the perception of under-treatment in the event of subsequent complications such as hospitalisation. There is systematic review evidence, now 15 years old, that antibiotics are ineffective for preventing complications.[1]
The NIHR 'TARGET' Programme for Applied Research has recently completed the recruitment of 8,500 children to a prospective cohort study to investigate the value of symptoms, signs and upper respiratory tract microbiology in predicting outcome, including: symptom duration, symptom severity, reconsultations and hospitalisations.

Aim: To investigate the effects of antibiotics to prevent hospital admissions in children with respiratory tract infections (RTIs)

Objectives:

1. To update a previously published systematic review[1] investigating the effects of antibiotics in reducing complications of RTIs
2. To use an existing dataset (TARGET Cohort Study) to identify the symptoms and signs that drive immediate and delayed antibiotic prescription in comparison with the symptoms and signs that drive hospitalisation
3. To evaluated the impact of no, immediate and delayed antibiotic use on symptom duration and severity (TARGET Cohort Study symptom diary data)
4. To investigate the effects of antibiotics use on reconsultations
5. To understand the impact of antibiotic use (including different antibiotic subtypes) on hospitalisation including an in-depth look at the timeline from presentation to taking of antibiotics to hospital admission
6. To work with the final TARGET Programme Workstream to conduct additional work which could include:
    a. An in-depth analysis of how the intervention affects antibiotic prescribing with reference to the low, intermediate and high risk groups.
    b. Collecting additional data asking GPs who prescribe antibiotics on a case by case basis to give their reason (using a drop-down box)
    c. To conduct qualitative interviews that ask parents and GPs about antibiotic prescribing

References:

1. Fahey T, Stocks N, Thomas T. Systematic review of the treatment of upper respiratory tract infection. Archives of Disease in Childhood 1998;**79**(3):225-30.

Supervisors/Collaborators:
Alastair Hay and Pete Blair

Title: Mathematical modeling of the impact of HCV vaccination among people who inject drugs

Background:

Hepatitis C virus (HCV) is a blood-borne disease that infects 150 million people worldwide and is a leading cause of liver disease. In developed countries, the main mode of transmission is amongst people who inject drugs (PWID) through syringe sharing.

HCV vaccines are currently in development and have shown promise for reducing infectivity or averting chronic infection[1,2]. One major vaccine candidate targeting genotype 1B has been shown to be well tolerated and highly immunogenic to this strain and less so to other genotypes[3]. Further studies are ongoing. Curative treatment for HCV also exists, and although new drugs have high efficacy (>90%) they are expensive and uncertainty exists on whether HCV vaccination will be effective following successful treatment, due to immune exhaustion.

We propose to develop dynamic models of HCV transmission among PWID[4-6] to evaluate the impact of HCV vaccination strategies. Different intervention setting (prison/community) will be considered as will the combined impact with other interventions. The novelty of the work will be in the model incorporating multiple genotype strains and the possible impact of HCV vaccination in two ways- protection against chronic infection and/or reducing infectivity.

Plan:

This project will consist of developing dynamic models of HCV transmission among PWID including vaccination and other interventions. The models will be used to evaluate:

1. The reduction in HCV transmission resulting from different vaccine coverage levels for varying vaccine characteristics (efficacy for different genotypes, duration of protection, and reduction in infectiousness)
2. The required vaccine coverage level needed for elimination in different HCV epidemic settings and for varying vaccine characteristics?
3. How HCV vaccination strategies should be combined with other interventions to increase impact and reduce the vaccine coverage needed for elimination?
4. The utility of different settings for undertaking HCV vaccination strategies amongst PWID, such as prison or addiction centres?
5. The impact of strategies where vaccination is provided post successful treatment? The effect of reduced vaccination efficacy due to immune exhaustion will be considered, as will different delays in vaccination to allow for immune recovery?
6. The implications of a vaccine only protecting for one strain. Is the vaccine's impact reduced due to the unprotected genotypes partially compensating, and how may the genotype distribution change over time?

Methods

This studentship will utilise mathematical modelling to understand HCV transmission, vaccination and prevention interventions. It will include training in how to set up and undertake research projects incorporating dynamic infectious disease transmission modelling. The candidate will gain experience in methods of infectious disease model development, parameterisation and fitting using Bayesian methods, and sensitivity/uncertainty analysis.

References:

1. Beamont, E. and R. P, *Prospects for prophylactic hepatitis C vaccines based on virus-like particles.* Hum Vaccin Immunother, 2013. **13**(9): p. 5.
2. Maher, L., et al., *Candidate hepatitis C vaccine trials and people who inject drugs: Challenges and opportunities.* Vaccine, 2010. **28**(45): p. 7273-7278.
3. Barnes, E., et al., *Novel adenovirus-based vaccines induce broad and sustained T cell responses to HCV in man.* Sci Transl Med, 2012. **4**(115): p. 115ra1.
4. Vickerman, P., et al., *Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in HCV prevalence? Model projections for different epidemic settings.* Addiction, 2012. **107**: p. 1984-1995.
5. Martin, N., et al., *HCV treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals.* Hepatology, 2013. **58**(5): p. 1598-1609.
6. Martin, N., et al., *Combination interventions to prevent HCV transmission among people who inject drugs: modelling the impact of antiviral treatment, needle and syringe programmes, and opiate substitution therapy.* Clin Infec Dis, 2013. **57**(suppl 2): p. S39-S45.

Supervisors/Collaborators:
Peter Vickerman, Matthew Hickman and Natasha Martin

Title: Mathematical modeling of an emerging epidemic: sexual hepatitis C transmission among HIV positive men who have sex with men

Background:

Hepatitis C virus (HCV) is a major cause of liver disease worldwide. In developed countries, HCV is predominantly transmitted through injecting drug use[1], and studies have shown that sexual HCV transmission between heterosexual couples is rare.

In recent years there has been a rapid spread of sexually transmitted HCV amongst HIV-positive men who have sex with men (MSM)[2,3], but little amongst HIV-negative MSM[4,5]. It is unknown why this emerging epidemic has occurred and why it is concentrated amongst HIV-infected MSM. This recent epidemic, along with a rise in HIV infections among MSM in the UK has resulted in increasing concern among the public health/medical communities[6].

Despite substantial literature on modeling HIV transmission among MSM[7] and HCV transmission amongst injecting drug users, no one has modeled sexual HCV transmission among MSM, and little is known about the transmission dynamics. This project would aim to develop both deterministic and network models of HIV and HCV transmission among MSM to explore how behavioural characteristics (such as risk heterogeneity, possibly based on HIV status, and assortative sexual mixing, where HIV positive men tend to have riskier sex with other HIV positive men) and biological characteristics (such as increased HCV viral load amongst HIV-HCV coinfected individuals and recent increases in survival of HIV infected men) drive the transmission of each disease and determine its patterns of spread.

The insights gained will increase our understanding of MSM risk behaviour and mixing, which will improve model projections of the coverage requirements for different prevention to reduce the transmission of both infections to low levels. The network models will be used to show how network characteristics determine the speed of the epidemic, and to identify optimal intervention allocation strategies among the network participants. The outputs of this project will shed light on the drivers of the emerging HCV epidemic among MSM, and shape policymaking surrounding intervention strategies.

Objectives:

1. Develop novel mathematical models (network and deterministic) of HIV and HCV transmission among MSM and fit to available data
2. Interrogate the drivers of HIV and HCV transmission among MSM, and determine which behavioural or biological characteristics contribute towards the patterns of disease transmission
3. Identify the most effective combination prevention strategies to reduce transmission of both infections to low levels

Methods:

This studentship will utilise various mathematical modelling techniques to understand HIV and HCV transmission and prevention interventions. It will include training in dynamic infectious disease transmission modelling including network and deterministic compartmental models. The candidate will also gain experience in methods of infectious disease model parameterisation and fitting using Bayesian methods, and sensitivity/uncertainty analysis.

References:

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infec Dis* 2005; 5(9): 558-67.
2. Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *AIDS* 2009; 23(12): F1-7.
3. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. *Gastroenterology* 2009; 136(5): 1609-17.
4. Price H, Gilson R, Mercey D, et al. Hepatitis C in men who have sex with men in London--a community survey. *HIV Med* 2013; 14(9): 578-80.
5. Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. *Sex Transm Infect* 2012; 88(7): 558-64.
6. Kirby T, Thornber-Dunwell M. New HIV diagnoses in London's gay men continue to soar. *The Lancet* 2013; 382(9889): 295.
7. Punyacharoensin N, Edmunds WJ, De Angelis D, White RG. Mathematical models for the study of HIV spread and control amongst men who have sex with men. *Eur J Epidemiol* 2011; 26(9): 695-709.

Supervisors/Collaborators:
Peter Vickerman, Matthew Hickman and Natasha Martin

Title: Factors Affecting Secondary School Staff's Mental Health

Background:

Teachers are consistently identified as being at elevated risk of psychological distress and mental disorder compared to the general working population. Explanations for this heightened risk of mental health problems have included the 'emotional labour' that teachers engage in, excessive workload, challenging student behaviour, lack of autonomy, and a culture of coping alone. However, no recent, good quality research has examined such explanations in detail, and although previously identified sources of stress may still be important, the changes that have occurred in the education system in recent years, possibly most significantly the move to become academies for many schools, may have created new challenges to staff mental health. Focusing on school staff mental health is not only important in its own right, given the increased risk of mental health difficulties, but it may also lead to an improvement in staff's ability to support students: school staff are increasingly expected to play a key role in the prevention and early detection of mental health problems in adolescence, and they have contact with more young people about mental health issues than any other public sector service.

Objectives of the study:

1. To review teachers' mental health compared to other occupations
2. To examine reasons for school staff's heightened vulnerability to poor mental health, focusing particularly on i) school processes and structures and how these impact on mental health ii) the academic year and whether there are key periods when staff mental health is particularly poor iii) any impact of changes brought about by academisation
3. To identify potential ways to reduce the risks to school staff's mental health

Proposed methods:

1. Secondary analysis of national datasets on occupations and health (e.g. Health and Safety Excecutive and ONS) to examine school staff's mental health relative to other occupations. 2. Qualitative case study work examining the sources of stress for school staff, including questions around academisation, school structures and processes, and seasonality of mental distress. This would include focus groups and interviews with a range of staff, and observations of meetings, lessons etc. 3. Use the findings from the case studies to identify examples of practice that are likely to promote good mental health among staff.

Supervisors/Collaborators:

Judi Kidger

Title: Waste water epidemiology – how can waste water analysis be incorporated or replace other epidemiological measures of substance use

Background:

Several demonstration projects have shown and proposed the analysis of communal sewage water entering wastewater treatment plants (WWTPs) as a new method for measuring trends in substance use, especially illicit drug consumption (1-4). Concentrations of drug target residues (DTRs) in wastewater can be measured with great accuracy and precision using state-of-the-art sensitive and robust analytical methods (5-6). Metabolites of alcohol consumption also in theory can be measured (7) In what has been termed the 'sewage epidemiology' approach, consumption of the parent drug is 'back-calculated' from these measured DTR concentrations (8).

However, the back-calculated quantity is an estimate, reliant on many assumptions and the reliability of several parameters. These include the size of the population served by the WWTP, the percentage of a dose of the parent drug that is excreted as the DTR, the route of administration of the parent drug, and frequency of drug use in the population. Typically to date only the analytical uncertainty in measurement of DTR concentrations in a sample has been taken into account (9). Since this uncertainty is generally very small, there is a great danger of over-interpretation of back-calculated drug consumption estimates (10).

Waste water epidemiology has potential to contribute evidence to three types of study. First, to provide data on trends and changes in drug consumption over time (e.g. to provide real time data on new synthetic drugs). Second, to provide information for estimating the prevalence of substance use (e.g. to support estimation of cocaine or heroin prevalence). Third, to provide evidence for natural experiments (e.g. to test changes in alcohol and drug policy in different geographical areas or before and after changes have occurred).

These back-calculations are performed independently for each of the two metabolites. We demonstrate in Section 3 that, using a slightly more sophisticated modelling approach based on Markov Chain Monte Carlo (MCMC) methods, both metabolites can be incorporated into a single analysis. We describe limitations of the presented analyses in Section 4, and consider the potential contribution of sewage epidemiology to prevalence estimation.

Plan:

The Phd proposal can make use of current and ongoing projects collecting waste water data in UK and other European settings in order to investigate and test:-

a) Benefits and limitations of using waste water to estimate prevalence of problem drug use – in particular heroin use.
b) How waste water data can be incorporated into prevalence estimation exercises and what impact could waste water data have on reliability of such prevalence estimation exercises.
c) Consider what sampling periods for waste water may be required to reduce uncertainty of annual measures of drug use prevalence (and reduce variability of daily/ weekly data collection).
d) Methods for analyzing trends in drug consumption over time.

Methods:

The student will develop statistical models including multiple parameter evidence synthesis and control chart methods.

References:

1. Frost, N., P. Griffiths, and R. Fanelli, *Peering into dirty waters: the potential and implications of a new approach to monitoring drug consumption.* Addiction, 2008. **103**(8): p. 1239-1241.
2. K. Thomas et al., Science of the Total Environment 432 (2012) 432
3. Zuccato, E., et al., *Estimating community drug abuse by wastewater analysis.* Environmental Health Perspectives, 2008. **116**(8): p. 1027-1032.
4. van Nuijs, A.L.N., et al., *Illicit drug consumption estimations derived from wastewater analysis: A critical review.* Science of the Total Environment, 2011. **409**(19): p. 3564-3577.
5. Baker, D.R. and B. Kasprzyk-Hordern, *Multi-residue analysis of drugs of abuse in wastewater and surface water by solid-phase extraction and liquid chromatography-positive electrospray ionisation tandem mass spectrometry.* Journal of Chromatography A, 2011. **1218**(12): p. 1620-1631.
6. Castiglioni, S., et al., *Evaluation of Uncertainties Associated with the Determination of Community Drug Use through the Measurement of Sewage Drug Biomarkers.* Environmental Science & Technology, 2013. **47**(3): p. 1452-1460.
7. M Reid et al., Alcoholism: Clinical and Experimental Research 35 (2011) 1593
8. Zuccato, E., et al., *Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse.* Environ Health, 2005. **4**: p. 14.
9. Baker, D.R., L. Barron, and B. Kasprzyk-Hordern, *Illicit and pharmaceutical drug consumption in the UK estimated via wastewater analysis. Part A: chemical analysis and community-wide drug use estimates.* Science of the Total Environment, 2014 (in press).
10. Jones H, Hickman M, Ades AE, Welton NJ, Baker D, Kasprzyk-Hordern B. Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B: Accounting for the multiple sources of uncertainty. Science of the Total Environment 2014 (under review)

Supervisors/Collaborators:

Hayley Jones, Matthew Hickman and Barbara Kasprzyk-Hordern

Title: An investigation of intra-uterine nutrition and prenatal development– applying the principle of Mendelian randomization

Background:

Heavy alcohol drinking during pregnancy can result in foetal alcohol syndrome, which is characterized in part by growth deficiency and neuro-developmental disorders. However the effects of moderate levels (within the normal range) of drinking on foetal development during are not clear. Similarly the effects of low levels of nutrient intake, for example folate and vitamin D, during pregnancy on infant development are not clear. The problem is that observational studies are often unable to control for confounding by smoking, other nutrients, socioeconomic status and other lifestyle factors. Measurement of duration and amount of intake may be inaccurate, due to wide categories, misreporting of intake and recall bias. Genetic variants have been identified which may influence exposure to alcohol and other dietary factors through effects on intake propensities and via differences in metabolism. These variants are likely to be distributed randomly with respect to other dietary and lifestyle factors, including smoking, and can be used as surrogates for measuring dietary intake. It would be of interest to determine whether such genotypes in the mother and foetus, are associated with developmental outcomes among infants and hence whether moderate alcohol consumption and low dietary intake of vitamins and other nutrients during pregnancy influences infant phenotypes. In addition understanding the influence of prenatal risk factors on childhood behaviour and psychiatric disorders requires some knowledge of the biological pathways mediating between these exposures and outcomes. One possibility is that gene expression is altered via modifications to the foetal epigenome, a phenomenon that has become the focus of considerable interest in recent times. Mendelian randomization can be used to interrogate the role of epigenetic processes in causal pathways to psychiatric (and many other) disorders.

Plan:

The plan is to assess associations between genetic variants related to diet among mothers and relate these to offspring development outcomes (including psychiatric and psychological outcomes), and also to determine whether epigenetics is likely to explain any observed associations.

Objectives:

1) Identify genetic polymorphisms, which metabolise nutrients, or affect exposure propensities and which may be related to development in utero.
2) Analyse associations between the above polymorphisms and prenatal development to determine which nutrients are important in a large cohort study.
4) Analyse associations between the above polymorphisms and markers of gene expression
5) Analyse associations between gene expression and outcomes of interest

Supervisors/Collaborators:

Sarah Lewis and Caroline Relton