

School of Social & Community Medicine



**Research student opportunities in Epidemiology and Health Services
Research 2011**

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Topics 2011

Epidemiology and Health Services Research

Title of Project: Modeling suicide trends over time and between countries

Outline of Project

Background

Suicide is one of the government's priority areas for reducing deaths¹ and accounts for a significant proportion of potential years of life lost². Two striking features of the epidemiology of suicide are the large variations in its incidence over time and international differences in these temporal trends. Within Europe the main source of recent concern is the rise in youth suicide and a key feature of recent population suicide trends has been the 2-3 fold rise in young male deaths in many, but not all, industrialised countries. Explanations for the differing patterns in suicide trends (by age and gender) between countries are unknown and a greater understanding of factors contributing to observed trends will provide crucial insights into (i) the causes of suicide, (ii) approaches to its prevention and (iii) likely future trends in incidence. An understanding of the influences on time trends in suicide is also important when judging the success or failure of national prevention strategies^{3,4}.

Aim

The aim of this studentship is to use a series of appropriate modeling approaches to identify explanations for differing European trends in suicide over the last 40 years of the 20th century. Candidate techniques include time-series analysis, join-point regression and age-period-cohort models.

Data

Data will be obtained from the WHO mortality database, UN Demographic Yearbooks, OECD Labour Force Survey and Historical Statistics and other relevant sources. All European countries for which age- and gender-specific suicide rates are available from 1960 onwards will be included in the analyses.

Methods

Time series models describe and explain observed trends in rates in terms of secular trend, seasonal variation, cyclical variation and irregular variation (for example, the seasonal component of suicide trends is well recognised⁵). Such an approach has already been applied to suicide rates in England and Wales⁶ and results will be compared across countries. Join-point regression analyses may identify, for each country, the year(s) in which trends in suicide rates change direction. Similar approaches have been applied to cancer mortality rates, providing clues to likely explanations for changes in secular trends⁷. As well as being a useful method of summarizing observed rates, a comparison between countries of join-point years may clarify likely factors precipitating these changes. Both these methods take calendar time as the independent variable, and will be applied separately to data sets for each age/gender/country group. A more complex approach recognizes time as acting in three dimensions – age, period (calendar time) and cohort (time of birth). Although problems arise in trying to estimate all these effects simultaneously, generalized linear models can be used to fit age-period and age-cohort models for each country/gender data set. Joint models can then also be fitted if either cohort or period effects are found to be similar for both males and females. This reduces the number of parameters and enables estimation of age, period and cohort effects in one model. The resulting estimates can be compared across countries. Furthermore, countries exhibiting similar trends may be grouped together in a joint model, further improving the precision of estimates. A Bayesian implementation of these models has been used to make projections of cancer rates⁸, and could equally be applied to suicide rates to predict future trends.

References

¹ Department of Health (1999). *Saving Lives: Our Healthier Nation*.

² Gunnell, D. & Middleton, N (2003). National suicide rates as an indicator of the effect of suicide on premature mortality. *Lancet*; 362: 961-2.

³ Department of Health (2002). *National suicide prevention strategy for England*. Department of Health, London.

⁴ US Department of Health and Human Services (2001). *National strategy for suicide prevention: goal and objectives for action: summary*. Rockville, MD.

⁵ Lester, D. (2001). *Suicide prevention: resources for the millennium*. Brunner-Routledge, Hove. p20.

⁶ Gunnell, D., Middleton, N., Whitley, E., Frankel, S., Dorling, D. (2003). Why are suicide rates in young men increasing? - a time series analysis of trends in England and Wales 1950-1998. *Soc Sci Med*; 57: 595-611.

⁷ Oliver S, May M, Gunnell D. International trends in prostate cancer mortality in the 'PSA era'. *Int J Cancer* 2001;92:893-898

⁸ Bray, I. (2002). Application of Markov chain Monte Carlo methods to projecting cancer incidence and mortality. *Applied Statistics*; 51: 151-63.

Supervisors

Professor David Gunnell
Department of Social Medicine

Title: Investigating and developing methods to improve the commissioning, design, and conduct of RCTs. (The MRC ConDuCT Trials Methodology Hub).

The MRC ConDuCT Trials Methodology Hub brings together research, into the commissioning, design and conduct of RCTs, being conducted in the University of Bristol Departments of Social Medicine and Community Based Medicine. The Hub has funding for five four-year PhD studentships, joint funded by the MRC and the University of Bristol. In the first year students will attend courses from Social Medicine's popular short course programme, and elsewhere, to build a comprehensive knowledge of RCT design and conduct. The first year will also provide the opportunity to conduct small studies in different areas of trials methodology, allowing students to confirm their area of interest, build their research skills, formulate a detailed research plan for the subsequent three years, conduct feasibility studies of intended research procedures, and meet and work with theme leads within the Hub.

Current and forthcoming areas of work are as follows:

- Developing and integrating qualitative research methods to improve the design and conduct of RCTs
- Statistical methods in the design and analysis of challenging RCTs
- Methods for dealing with missing data, baseline covariates and incorporating productivity costs in economic evaluations conducted alongside RCTs
- Improving trial conduct
- Embedding clinically meaningful patient reported outcomes into RCTs

Many hub members are also involved with the Bristol Randomised Trials Collaboration, which has links with many ongoing and recently completed RCTs.

Supervisors: *These include:*

Social Medicine: Jane Blazeby, Sara Brookes, Rona Campbell, Jenny Donovan, Will Hollingworth, Athene Lane, Chris Metcalfe, Sian Noble, Jonathan Sterne, Kate Tilling.
Community Based Medicine: Tony Ades, Alison Heawood, Sandra Hollinghurst, Alan Montgomery, Tim Peters, Nicky Welton, Nicola Wiles

Title: Using qualitative methods at the end of randomised controlled trials to evaluate the utility and implementation of trial results

The value of integrating qualitative methods within randomised controlled trials is increasingly recognised, particularly by health services researchers conducting pragmatic community-based trials. To date, qualitative methods (particularly interviews, but also observations and recordings of appointments) have been used at various stages of the trial process, notably during and pre trial. A reasonably common use is for the evaluation of patients' experiences of interventions prior to or during a trial to inform understanding of the acceptability of such interventions (Beattie et al, Emmett et al). Qualitative methods are increasingly used as part of process evaluations during trials, with the aim of improving the quality of trial conduct. Particular attention has been given to how qualitative research can help improve patient recruitment to trials. For example, some qualitative work has investigated clinicians' experiences of recruiting patients to a trial within consultations, identifying barriers and facilitators to patient recruitment (Mason et al 2007). Multiple qualitative methods (including in-depth interviews with RCT participants and recruitment staff, and analysis of information exchanged by recruiters and participants within recruitment appointments) have been used in a trial facing recruitment difficulties with the result of increasing patient acceptance of allocation and randomization rates (Donovan et al 2002, Donovan et al 2008). Early attempts have been made to implement this qualitative package (in the form of a complex intervention) in other trials facing recruitment difficulties, albeit with some challenges, including difficulties establishing collaboration between the qualitative team and RCT staff, poor communication between trial principal investigators and recruiting staff, and recruiters' concerns about having recruitment appointment recorded (de Salis et al 2008, 2008).

Qualitative methods are also increasingly being used within pre-trial feasibility studies, to elucidate and overcome potential process difficulties, and determine appropriate outcome measures, prior to starting the full trial. Such use of qualitative methods was recommended within the Medical Research Council's Framework for evaluating complex interventions (Campbell et al). Yet to date, little attention has been given to the use of qualitative methods at later stages of trials, particularly in relation to the implementation of trial results. This is important as while a trial may produce clinically and statistically significant results, these results may or may not receive recognition or be implemented in the relevant clinical settings. Therefore, the focus of the proposed PhD is to explore how qualitative methods may be incorporated in this post-trial phase to evaluate how trial results are received and implemented, with the ultimate aim of improving the utility of trial results.

Aim

To explore how qualitative methods can be used at the end of randomised controlled trials to evaluate the implementation and utility of trial results.

Methods

- Qualitative case study approach using a mixture of qualitative methods
- Selection of three ongoing/completed trials to act as 'case studies', drawn from trials within COBM or Social Medicine
- Sample of case studies to vary along certain criteria such as: clinical topic, setting in which trial was conducted, setting in which results may be implemented (may be same as trial setting), audience for the results (may overlap with former), fora/journals where results have been published, how 'controversial' the results are.
- Case studies would be staggered, so start with one or two trials that are in the public domain and have another near completed trial as the third case
- Possibilities for data collection:
 - Interviews or focus groups e.g. with clinicians/staff in settings where results are relevant and could potentially be implemented, the trial staff (such as PI, researchers and data analyst); journal editors or reviewers, others

- Documentary analysis e.g. of responses to publications in journals, trial management group/steering group meeting minutes where dissemination is discussed, written feedback of trial results to various audiences, final reports written by the trial team plus reviewer's comments
- Observation e.g. observation of end-of-trial management group/steering group meetings where dissemination strategies are discussed, observation of trial feedback meetings where results are disseminated to different audiences (e.g. clinical staff, policy/decision-makers), and leading conferences.

References

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Donovan J, Mills N, Smith M. *et al.* Improving the design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *British Medical Journal* 2002;325:766-770.

Emmett C, Shaw A, Montgomery A, Murphy D on behalf of the DiAMOND study group. Women's experience of decision making about mode of delivery after a previous caesarean section: the role of health professionals and information about health risks. *British Journal of Obstetrics and Gynaecology* 2006;113:1438-1445.

Mason VL, Shaw A, Wiles NJ, Mulligan J, Peters TJ, Sharp D, Lewis G. GPs' experiences of primary care mental health research: a qualitative study of the barriers to recruitment. *Family Practice* 2007;24:518-525.

Supervisors: *These include:*

Primary supervisor: Dr Alison Heawood, Academic Unit of Primary Health Care, School of Social & Community Based Medicine.

Secondary supervisor: Prof Jenny Donovan, School of Social & Community Based Medicine.

Title: Determinants and sequelae of sexual and risk behaviours during adolescence

Outline of Project

Background

Recognised sequelae of early romantic and sexual behaviours include teenage pregnancy and sexually transmitted infections (STIs). It has also been reported that early involvement in dating is associated with behavioural problems and lower psychosocial functioning. Most studies of adolescent sexual activity are cross-sectional. The use of data from longitudinal cohort studies will allow us to study the development of romantic and sexual behaviours from early adolescence onwards, and establish whether the trajectory of sexual development can be characterised into broad patterns.

An initial analysis of the ALSPAC data shows that although only a small proportion of adolescents are sexually active at age 12-13, romantic relations begin early, with 24% of 11-12 year olds and 41% of 12-13 year olds reporting having held hands, and 17% of 11-12 year olds and 32% of 12-13 year olds reporting having been kissed on the mouth (Waylen, Journal of Early Adolescence, under review).

There are currently two major public health initiatives in the area of sexual health. A national Chlamydia screening programme was introduced in 2006 for all young people under 25 years (www.chlamydia-screening.nhs.uk/). During the 17+ ALSPAC clinics, participants will be offered a Chlamydia screening test, and will be asked to consent to their urine sample to be stored for future STI testing. In 2008, a programme of vaccination against human papillomavirus (HPV), the infection which causes cervical cancer, was launched (www.immunisation.nhs.uk/Vaccines/HPV). The vaccine is being offered to girls up to age 18 as part of the catch-up programme; the girls in the ALSPAC cohort will be eligible for vaccination.

We hypothesise that there are likely to be early behaviours that are related to the prevalence of Chlamydia infection and the uptake of HPV vaccination.

Objectives

1. To describe romantic and sexual behaviour, and their trajectories, from age 11 onwards
2. To investigate associations between adolescent sexual behaviours and other early life factors (such as socioeconomic background, parental attitudes)
3. To investigate determinants of chlamydia screening/ HPV vaccine uptake in the ALSPAC cohort

Students will be encouraged to incorporate elements of interest from the above objectives, and to add their own ideas within the broad subject area of sexual behaviour during adolescence.

Data

Prospective data on romantic relations and sexual behaviour have been collected in the Avon Longitudinal Study of Parents And Children (ALSPAC) cohort from age 11 onwards. This is complemented by a comprehensive set of data on pubertal development, socioeconomic background and possible maternal and paternal influences on a child's attitude to early sexual activity. Data on chlamydia screening uptake will be collected at the age 17+ clinics and HPV vaccine uptake will be obtained through linkage to Primary Care Trust records (ethical approval or exemption will be sought within the framework of a broader data linkage project in ALSPAC).

Methods

The student will be encouraged to develop a work plan based around their interests. The project may therefore incorporate a range of quantitative and qualitative methods. Statistical

methods may include: descriptive statistics, linear, logistic and Cox regression modelling, structural equation modelling.

Potential supervisors

Please contact Dr Mona Jeffreys in the first instance. A range of potential supervisors within the School/ University may be involved depending on the particular direction taken by the student. These include, among others, Dr John Macleod, Dr Andrea Waylen, Dr Caroline Trotter, Dr Matthew Hickman, Dr Paddy Horner and Dr Ardiana Gjini.

(Mona Jeffreys is currently on maternity leave please contact Andrea Waylen)

Title: Ethical aspects of epidemiological research on young people involving linkage to routine individual data

Outline of Project:

Background

The Department of Social Medicine has recently obtained funding from the Wellcome Trust to undertake a significant research study which will substantially enhance the value of the data currently held by the Avon Longitudinal Study of Parents and Children (ALSPAC). Specifically, the study will involve linking its data with other national and health-care databases (record linkage). An important component of this project is the enriching of the ALSPAC database with data from external sources, including potentially sensitive social data such as criminal records.

This study raises several ethical issues, for example participant consent and issues in data linkage. These will be explored by way of a doctoral project that draws on and feeds into the wider research study. The doctoral project will particularly consider issues around different modes of consent to record linkage and questions of public good versus individual privacy in epidemiological research. Themes that may be drawn on in this project include modes of consent ('opt in' or 'opt out') and whether time limits to the validity of consent are important. The tension between the rights of individuals when compared with the potential benefit to society from record linkage will also be evaluated. Finally, the relevance and value of privacy and confidentiality will be explored.

Aims of the PhD

This doctoral project will address some of the ethical implications that may arise in the record linkage project described above. This will involve liaising with the wider research team and ensuring opportunities for empirical research are optimised. The doctoral project will aim to:

1. Scope the ethical issues arising in the record linkage project;
2. Synthesise existing literature on these issues;
3. Develop an appropriate strategy for empirical research on these issues with members of the ALSPAC cohort and possibly also researchers and the wider public;
4. Analyse research data for emergent themes;
5. Synthesise themes together with relevant scholarship in bioethics; and
6. Develop recommendations about appropriate methods of consent and record linkage to social data in cohort studies like ALSPAC. These will then be fed into the wider project, including training modules.

Methods

This will be a multi-disciplinary project, combining qualitative research with theoretical bioethics (applied philosophy). Research training will be provided for either or both of these research domains if required. The qualitative research will be undertaken together with the other qualitative streams in the wider research study. The research, as described in the 'Aims' section above, will address ethical themes such as consent and linkage to criminal records. This research can be undertaken with a variety of stakeholders. Data will be analysed for emergent themes but will also then be compared and critically analysed with respect to existing ethical literature and theoretical reasoning.

References

1. Huang N, Shih S-F, Chang H-Y, and Chou Y-J. Record linkage research and informed consent: who consents? *BMC Health Serv Res.* 2007; 7: 18.
2. Tate AR, Calderwood L, Dezateux C, Joshi H. Mother's consent to linkage of survey data with her child's birth records in a multi-ethnic national cohort study. *Int J Epidemiol.* 2006 Apr;35(2):294-8.
3. Hogue CJ. Ethical issues in sharing epidemiologic data. *J Clin Epidemiol.* 1991;44 Suppl 1:103S-107S.

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5. Privacy, epidemiology, and record linkage. *Br Med J.* 1979 Oct 27;2(6197):1018.
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More general ethics literature around issues of privacy, confidentiality and disclosure in research will also be relevant to this work.

Name of potential supervisors

Dr Ainsley Newson, Centre for Ethics in Medicine, University of Bristol
Catherine Heeney, Ethox, University of Oxford

Professor Rona Campbell and Professor John Macleod from the School of Social & Community Based Medicine will act as advisers to the project.

Title: Social inequalities in cancer risk factors, incidence and outcomes: a cross cohort analysis

Outline of Project:

Background

There is a large body of literature documenting gradients in cancer risk factors (e.g. BMI, smoking), cancer incidence, and cancer survival across socio-economic groups. However, our understanding of the point across the life course at which these inequalities arise, and hence the best opportunities for intervention, remains limited. Furthermore, the role that inequalities in cancer risk and prognostic factors play in determining cancer outcomes had not adequately been addressed.

Aims of the PhD

1. To conduct a systematic literature review on the role that the socio-economic gradient in risk factors plays in determining the socio-economic gradient in cancer outcomes.
2. To identify from this the key site-specific cancers, and associated risk factors, on which the remainder of the PhD will focus.
3. To analyse data collected in various Bristol-based and other cohorts to investigate the relative importance of timing of deprivation in relation to the social patterning of cancer-related risk factors and outcomes.
4. To estimate the reduction in inequalities in cancer that could be achievable through reduction in inequalities in risk factors.

Data

The Department of Social Medicine hosts a wide range of cohort studies and has strong collaborative links with other UK-based and international cohorts with potentially relevant data. The idea behind the cross-cohort approach is that the data have been collected at different points of the life course, as well as at different periods. Thus, there are pertinent data from childhood (e.g. Boyd Orr, ALSPAC), adolescence (ALSPAC, Christ's Hospital Cohort), young adulthood (ALSPAC, Glasgow, Barry Caerphilly), and later adulthood (Caerphilly, Speedwell, Glasgow, ProtecT).

Anticipated methods

The candidate will be expected to become proficient in the use of conventional statistical methods in epidemiology, including, as appropriate, multivariable linear, logistic and Cox proportional hazards regression. Systematic review methods will be used; the School holds a 3-day course on systematic reviewing and meta-analysis every year. If interested, there will be possibilities for more advanced statistical modelling.

Supervisors: Mona Jeffreys, Yoav Ben Shlomo, John Lynch

(Mona Jeffreys is currently on maternity leave please contact Yoav Ben-Shlomo or John Lynch)

Methods

Standard statistical methods for cross-sectional and longitudinal studies will be used. Analyses of risk factors will use multivariable approaches to identify specific risk factors for suicidal thoughts and depression. The student will get experience of analysing a large linked dataset. Additional linkage opportunities include the possibility of linking HUNT data to the national prescription register to identify use of antidepressants and tranquilisers in Young HUNT-3.

Supervisor: Prof David Gunnell and other supervisors drawn from the School of Social & Community Based Medicine and the HUNT Research Group: Turid Holmen; Ottar Bjerkeset; Hans Nordahl; Pal Romunstad

References

Bjerkeset O, Romundstad P, Evans J, Gunnell D. The association of adult body mass index and height with anxiety, depression, and suicide in the general population: The HUNT study. *Am J Epidemiol* 2008; 167: 193-202.

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<http://www.med.uio.no/ipsy/ssff/statistikk/pdf/Gjertsenstatistiskeoppgaverselvmordmai07.pdf>
(Internet Publication 2nd May 2007)

Reseland S, Bray I, Gunnell D. Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries. *Br J Psychol* 2006; 188:354-358

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 $\frac{3}{4}$ 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 what 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:-

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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: Examining the relationship between cannabis use, psychosis and depression in ALSPAC

Outline of project:

Applications are invited from suitably qualified graduates to join a team investigating the development of psychotic and depressive symptomatology from late childhood through adolescence. The PhD will be undertaken in the Academic Unit of Psychiatry and will focus on examining the relationship between cannabis use, psychosis and depression in the ALSPAC birth cohort.

There is some evidence that cannabis use can lead to an increase in psychotic phenomena, though evidence for a causal effect on depression is weaker. Furthermore, the relationship between such psychopathology and substance use is complex and likely to be operating in both directions, as well as possibly confounded by other characteristics of individuals who use drugs and suffer from mental health problems. The project will focus on examining the strength of evidence in support of a causal relationship between cannabis use and both psychosis and depression, independent of any confounding effects, as well as examining potential mechanisms such as changing social relationships or social cognition that might mediate such a relationship.

The PhD student will have the opportunity to develop skills in multivariable statistical modelling of longitudinal data with repeated measures. They will benefit from the expertise available within the department, as well as through close links with other researchers working in ALSPAC. 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>

Supervisors:

Stanley Zammit, Academic Unit of Psychiatry

Matt Hickman, School of Social & Community Based Medicine

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 COPD¹. 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 FEV₁, maximal mid-expiratory flow (MMEF) reflecting small airways obstruction, and FEV₁/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 adjusted 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: Modelling the natural history of multiple sclerosis and examining potential prognostic risk factors

Outline of project:

Multiple sclerosis is a chronic neurodegenerative disorder that starts in young adulthood and has a variable prognosis but in general progresses over time resulting in increased disability, reduced quality of life and excess-related mortality. Clinically patients are usually categorized into three distinct groups based on their presentation. These are (a) relapsing relapsing MS (RRMS) where patients have acute neurological episodes which usually get better and may or may not leave any residual problems, (b) primary progressive MS (PPMS) where patients present usually with a slow insidious decline in functional abilities and (c) secondary progressive MS (SPMS) which usually follows PPMS and where relapses may or may not still occur but there is evidence of clinical decline independent of relapses. Whether these different patterns reflect different disease sub-groups or are merely different manifestations of the same underlying pathology but related to age at onset¹ remains controversial and of great interest. Several prospective clinical cohorts have identified potential prognostic factors that may help predict the clinical course of disease. These include age at onset, gender, and frequency of relapses for RRMS. However these findings are not always consistent across cohorts. More recently the identification of genetic markers of MS risk from GWAS highlight potential candidates for prognostic markers and other biomarkers, such as MRI features at presentation have also been suggested. The need to differentiate patients with slower from more aggressive disease patterns is of major importance as new “disease modifying therapies” (DMT) are emerging² which may alter the natural history by enabling repair but are themselves associated with some risk both in the short term and potentially in the longer term if they alter the body’s natural defence systems against neoplasia.

Objectives:

1. To undertake a systematic review (with or without a meta-analysis) on the natural history and prognostic markers in MS
2. To use sophisticated statistical methods to model the natural history of MS and examine whether there may be distinct sub-groups or whether age at onset explains variability.
3. To examine for prognostic markers of disease course and derive a prognostic algorithm that may be helpful for clinical trials or patient counselling and advice

Methods:

The project will be based on a large MS register based in the University Hospital of Wales (UHW, Cardiff) and led by Dr. Neil Robertson. The University Hospital of Wales (UHW) is the major tertiary referral centre for neurology in Wales serving a local population of 1.2 million. The department of neurology has provided a network of MS clinics across South East Wales since 1999 and additional clinical data is available on patients from 1985.

Approximately 1000 patient contacts are currently documented annually and demographic and clinical data collected routinely at presentation with minimum subsequent current status data sets at each visit including current disease course (classified according to relapsing remitting (RR) secondary progressive (SP) or primary progressive (PP)) and relapse status, expanded disability status score (EDSS) (21), therapeutic interventions together with site and timing of relapses since last review. Initial and subsequent complete datasets are available on 1270 patients with MS comprising more than 90% of the local prevalent patients and may therefore be considered to be a representative sample of the prevalent population. Data on specific features of disease onset are available such as age of first event, age at diagnosis, reported clinical features at first event (split into isolated sensory, longitudinal tract, cerebellar, brainstem, optic neuritis, unifocal or multifocal features) and recovery from first event (either full recovery, incomplete recovery or progressive disease from onset). It has already published epidemiological data on the cohort.³

We will examine a variety of statistical methods, including multi-level and latent trait models to explore how well one can explain the heterogeneity of disease progression. Specific clinical features will be explored to see if they have prognostic value. Findings that look promising will be tested, if possible using independent secondary datasets (with permission of the respective PIs) such as the MS-RSS and the British Vancouver register.

The implications of these findings will be explored in relation to inclusion criteria for RCTs and sample sizes as well as the ability to risk stratify for therapies and counselling.

The PhD student will be supervised by YBS (clinical epidemiologist) KT (senior statistician) and NR (MS specialist neurologist and custodian of dataset)

References:

1. Confavreux C et al Age at disability milestones in MS. *Brain* 2006;129:595-605
2. The CAMMS223 Trial Investigators. Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis. *NEJM* 2008 Volume 359:1786-1801
3. Hirst C et al. Change in disability in patients with multiple sclerosis: a 20-year prospective population-based analysis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2008;79:1137-1143

Supervisors: Yoav Ben-Shlomo, Kate Tilling, Neil Robertson

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 social 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 publication February 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: What is the long-term effect of childhood milk intake on adult health?

Outline of Project:

Background

In industrialised countries milk is an almost universal exposure particularly in childhood, and dietary guidelines in Europe and the USA make recommendations about appropriate levels of intake. However, milk is a food designed for infants and the long-term health effect of its consumption beyond infancy in well-nourished populations is unclear.

High levels of milk intake in childhood are associated with accelerated linear growth. Insulin-like growth factors (IGF-I) are thought to mediate this association. The long-term effects of childhood milk intake on adult health are less certain. Research suggests that adults who consume high levels of milk may be at an increased risk of prostate cancer, but have a lower risk of colorectal cancer, cardiovascular disease and overall mortality. The situation in relation to childhood milk intake may be quite different. An emerging body of evidence from Bristol-based as well as other international studies indicates that milk intake in childhood may programme the IGF system to produce low levels of IGF-I in adulthood. Such low levels are thought to be associated with an increased risk of cardiovascular disease.

Aims of the PhD

- To review the literature on the association of childhood milk intake, and genetic polymorphisms influencing milk intake, with a range of adult health outcomes; particularly overall mortality, cardiovascular disease, cancer and cognitive decline.
- To analyse data collected in various Bristol-based and other cohorts to investigate the association of childhood milk consumption and milk supplementation with adult health outcomes, particularly: all-cause mortality, cancer and cardiovascular disease.

Data

The Department of Social Medicine hosts a wide range of cohort studies and has strong collaborative links with other UK-based and international cohorts with potentially relevant data. One component of the investigations is likely to be the Boyd Orr cohort [1]. Over 1,000 members of this cohort of around 5,000 men and women who were originally studied in the 1930s took part in a controlled diet supplementation study. The supplements they received included milk and previous analysis of the dataset has shown that supplementation had a beneficial impact on childhood growth [2]. Other relevant cohorts include ALSPAC [3], and other National Birth cohort studies.

Anticipated methods

Conventional systematic review methods will be used; the Department holds a 3-day course on systematic reviewing and meta-analysis every year. Cohort analyses will use appropriate multivariable modeling techniques including logistic and Cox proportional hazards regression. These methods are both covered in detail in the Department's short course program. The Department is currently developing a wide-ranging genetic epidemiology program and some of the research questions may also be pursued using appropriate Mendelian randomization approaches.

Supervisors: Richard Martin, David Gunnell

Title: Incorporating Covariates in Cost-Effectiveness Analysis of RCT Evidence

Background

It is standard practice in the analysis of effectiveness data from Randomised Controlled Trials (RCTs) to adjust for covariates that may potentially be confounded with the treatment effect size. Various methods for covariate adjustment of cost-effectiveness data have been recently described^{1,2}, although they have yet to become standard practice.

In order to inform policy decisions, cost-effectiveness analyses should report incremental costs and effects averaged over the population in which a treatment decision is to be made. Therefore, appropriate covariate adjustment of cost-effectiveness results requires integration over the joint distribution of covariates.

Research Questions

The aim of the PhD is to: (i) explore the role of covariates in cost-effectiveness analysis modelling, (ii) develop methods for the joint modelling of covariates and (iii) investigate different methods for integration over the covariate distributions in the cost-effectiveness analysis.

References

1. Willan A, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ.* 2004 May;13(5):461-75

Nixon RM, Thompson SG. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health Econ.* 2005 Dec;14(12):1217-29.

Primary supervisor: Nicky Welton, School of Social & Community Based Medicine

Secondary supervisor: Will Hollingworth, School of Social & Community Based Medicine

Title: The net benefit regression framework for estimating cost effectiveness in randomised trials

Background

The net benefit approach to cost effectiveness analysis is a relatively new development which has seen widespread adoption only in the past few years (Stinnett & Mullahy, 1998). Incremental net benefit is a measure of cost-effectiveness that can be estimated using standard regression models. Consequently there is the potential to take those statistical methods developed within the regression framework and apply them to cost-effectiveness analysis. So far this has led to regression methods for subgroup comparisons and covariate adjustment being applied to cost-effectiveness data (Willan, Briggs & Hoch, 2004).

Potential research questions

Estimates of cost-effectiveness in those adhering to their allocated treatment. In comparisons of a novel and a standard intervention, it is common for a number of participants allocated to the novel intervention to in fact receive the standard intervention. An intention to treat analysis will typically underestimate the effect of the novel treatment in those who are able to adhere to it, whilst the difference in costs may be under or overestimated. Propensity score (Joffe, Ten Have & Brensinger, 2003) and complier-average causal effect analyses (Dunn, Maracy & Tomenson, 2005) have been developed for the unbiased estimation of treatment effects; the net benefit approach may allow these methods to be applied to cost-effectiveness analysis.

Estimates of cost-effectiveness in cluster-randomised trials. Difficulties encountered in estimating cost-effectiveness ratios from cluster-randomised trial data may be avoided by the net benefit approach (Flynn & Peters 2005a, 2005b). The clustered structure of the data, and the distribution of the net benefit measure will both need to be accommodated. Multi-level models have been developed for international studies (Grieve et al, 2007), although issues around the routine use of these models are likely to require work.

References

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- Flynn TN, Peters TJ. Cluster randomized trials: Another problem for cost-effectiveness ratios. *International Journal of Technology Assessment in Healthcare* 2005a; 21:403-409.
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- Grieve R, Nixon R, Thompson SG, Cairns J. Multilevel models for estimating incremental net benefits in multinational studies. *Health Economics* 2007; 16:815-826.
- Joffe MM, Ten Have TR, Brensinger C. The compliance score as a regressor in randomized trials. *Biostatistics* 2003; 4:327-340.
- Stinnett AA, Mullahy J. A new framework for the analysis of uncertainty in cost-effectiveness analysis. *Medical Decision Making* 1998; 18 suppl:S68-S80.
- Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Economics* 2004; 13:461-475.

Primary supervisor: Dr Chris Metcalfe, School of Social & Community Based Medicine

Secondary supervisor: Dr Will Hollingworth, School of Social & Community Based Medicine

Title: Understanding factors that reduce follow-up in randomised trials and assessing methods to enhance follow-up

Background

Participant retention in long term follow-up is the greatest challenge to the successful conduct of randomised trials following recruitment. Differential attrition from the randomized groups (especially if related to outcome) can have a significant impact on study findings by generating a null result (type II error). The UKCRN, UK trial managers and a recent American systematic review have all highlighted the need for good follow-up (Robinson K JCEpi 2007;60:757). Currently however, there are few strategies for retaining participants that have been evaluated empirically.

The focus of the research is to establish the current best practice from the trial and epidemiological cohort literature and a survey of registered trials units which will also establish the types of trials viewed as challenging for follow-up. In parallel, qualitative research will investigate the barriers to follow-up with key stakeholders. This research will be used to develop a package of measures to enhance follow-up which will then be evaluated in range of clinical trials.

Aim

To use a mixed methods approach to understand the barriers to retention of participants in trials and to design methods to improve follow-up across a variety of trial settings and disease sites.

Methods

- Systematic literature review to summarise current best practice of follow-up in RCTs and cohort studies
- Survey the 40 UKCRN registered trials units for successful follow-up strategies and trials viewed as challenging to follow-up
- Utilise qualitative research methodology with participants, trialists and clinicians to establish the barriers to follow-up across a range of trial settings, disease areas and follow-up methods

Develop a package of measures to enhance follow-up and evaluate these measures within collaborating trials taking into consideration the logistical and resource implications for trials

Primary supervisor: Dr Athene Lane, School of Social & Community Based Medicine

Secondary supervisor: To be arranged

Title: Optimising the statistical precision of economic evaluations conducted alongside RCTs

Background

Many randomised controlled trials (RCTs) now collect resource use as well as patient outcome data to provide evidence on cost-effectiveness to aid policy makers. However, the sample size of RCTs is almost always based on achieving statistical power on the primary clinical outcome rather than on cost-effectiveness. Sample size calculations for cost-effectiveness have been derived[1], but these are rarely used in practice, in part due to the lack of pilot data on the mean and distribution of costs. Cost data often exhibit non-normal distributions with high variance[2]. Therefore, it is often assumed that RCTs are generally severely underpowered on economic outcomes, but there is little empirical evidence to substantiate this[3].

A better understanding of the impact of incorporating economic data in RCTs, due to cost variance, cost/effect covariance, and ‘minimally economically important differences’, is essential for research funders and practitioners designing trials. It may also influence other aspects of trial design (e.g. stopping rules) and analysis (e.g. adjustment for baseline covariates).

Research Questions

Potential elements of this PhD project include:

1. A review of current sample size calculations for cost-effectiveness.
2. Review UK trial data on the degree of cost variance and cost/effect covariance stratified by type of intervention (e.g. therapeutic/ diagnostic/ preventative), setting of care (e.g. community, outpatient, inpatient), and duration of follow up.
3. Identify RCTs that have collected data on costs and outcomes and were published in leading medical journals. Calculate (post-hoc) the statistical power of each study to detect an “important” difference in effects and cost-effectiveness (i.e. net monetary benefit).
4. Collaborate with a ConDuCT randomised controlled trial to predict statistical precision based on the above reviews and collect pilot cost-effectiveness data to refine sample size calculations for the main trial.
5. Use individual patient data from existing cost-effectiveness RCTs to estimate the impact on statistical precision of adjusting for baseline covariates.

References

- [1] Walter SD, Gafni A, Birch S. Estimation, power and sample size calculations for stochastic cost and effectiveness analysis. *Pharmacoeconomics*. 2007;**25**:455-466.
- [2] Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? *BMJ* 2000;**320**:1197-1200.
- [3] Backhouse ME. Use of randomised controlled trials for producing cost-effectiveness evidence: potential impact of design choices on sample size and study duration. *Pharmacoeconomics*. 2002;**20**:1061-1077.

Primary supervisor: Dr Will Hollingworth, School of Social & Community Based Medicine.

Secondary supervisor: Chris Metcalfe, School of Social & Community Based Medicine

Title: Estimating productivity changes for economic evaluation

Background

Productivity costs have been defined as the productivity lost and/or the costs incurred to maintain productivity as a result of a worker's illness and its treatment.¹ Changes in productivity will occur when employees take time off work because of ill health, to receive healthcare, or to care for family or friends.

The inclusion of productivity changes in economic evaluation is contentious for a number of reasons. Drummond² identifies four main areas of concern: (i) lack of agreement about the best method of valuing changes in productivity; the two methods most widely used are the human capital approach and the friction cost approach, (ii) the extent of 'double counting' of benefits arising from increased productivity if the outcome measure is utility, (iii) whether indirect non-healthcare costs should be included if outcomes are health-related, and (iv) equity considerations around the valuation of productivity changes.

In response to these concerns, some general guidelines have been proposed as to how best to deal with productivity changes in an economic evaluation.² They provide some consistency in approach but there is little evidence that they have been used in empirical work. Additionally, there has been no evaluation of these recommendations and no investigation into their appropriateness in different specific settings. For example, a condition that prevents a small number of patients from working for long stretches of time will result in a very different pattern of lost productivity than one that is highly prevalent but results in just a few days off work at a time.^{3,4} And conditions that are more prevalent in specific patient groups, defined by, say, age or sex, may affect productivity differently than those affecting the general population.⁵

Research Question

This research will:

- conduct a review of existing guidance on the inclusion of productivity costs
- investigate the extent to which the current recommendations have been acknowledged and used in published
- identify scenarios for which general guidelines around dealing with productivity losses and gains may be inappropriate
- model productivity losses and gains for these scenarios
- refine existing guidelines in the light of the results

References

- [1] Koopmanschap M, Burdorf A, Jacob K, Jan Meerding W, Brouwer W, Severens H. Measuring productivity changes in economic evaluation. *Pharmacoeconomics* 2005; 23: 47-54
- [2] Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the economic evaluation of health care programmes*. Oxford Medical Publications, 2005
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- [4] Brouwer W. How to calculate indirect costs in economic evaluation. *Pharmacoeconomics* 1998; 13: 563-566
- [5] Olsen J, Richardson J. Production gains from health care: what should be included in cost-effectiveness analyses? *Social Science and Medicine* 1999; 49: 17-26

Primary supervisor: Dr Sandra Hollinghurst, Academic Unit of Primary Health Care.

Secondary supervisor:

Dr Sian Noble, Department of Social Medicine

Title: The use of routine data in trial based economic evaluations

Background

The increased use of trial based economic evaluations to provide evidence on cost-effectiveness has highlighted missing data as being a particular methodological issue.¹ One which arises because the total cost for a person is calculated from individual cost components and is compounded because of the skewness of the cost data. The approach to the handling of such missing data is complicated and as the complexity of RCTs increases so does the handling of such data.

One obvious way to overcome this issue is to initially obtain a complete or near complete dataset. In relation to NHS resource use, when GP records and Hospital notes are used to extract information on patient resource use then a complete dataset can be obtained.² This process is however time consuming and therefore expensive especially in multi-centred long term trials.

Ideally in England and Wales the use of routine data sources akin to the Scottish Morbidity Records³ would be one way of reducing this expense. One source of routine secondary care data in England and Wales which could potentially be used in trial based economic evaluations is the HES (Health Episode Statistics) database.

Research Questions

Potential elements of this PhD project include:

1. A review of the use of routine sources in trial based economic evaluations.
2. Comparison of the hospital resource use obtained from a sample of men in the Comparison Arm for ProtecT study, with information obtained for these men from the HES database.
3. Estimating the costs of obtaining these data from the two sources.
4. Evaluating whether HES can be used as a routine source of data for trial based economic evaluations.

References

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Primary supervisor: Dr Sian Noble, School of Social & Community Based Medicine.

Secondary supervisor: Dr Sandra Hollinghurst, Academic Unit of Primary Health Care, School of Social & Community Based Medicine

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-making¹⁻³. 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 yield⁴. 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-making⁵.

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

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

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

Title: Using qualitative methods at the end of randomised controlled trials to evaluate the utility and implementation of trial results

Background

The value of integrating qualitative methods within randomised controlled trials is increasingly recognised, particularly by health services researchers conducting pragmatic community-based trials. To date, qualitative methods (particularly interviews, but also observations and recordings of appointments) have been used at various stages of the trial process, notably during and pre trial. A reasonably common use is for the evaluation of patients' experiences of interventions prior to or during a trial to inform understanding of the acceptability of such interventions (Beattie et al, Emmett et al). Qualitative methods are increasingly used as part of process evaluations during trials, with the aim of improving the quality of trial conduct. Particular attention has been given to how qualitative research can help improve patient recruitment to trials. For example, some qualitative work has investigated clinicians' experiences of recruiting patients to a trial within consultations, identifying barriers and facilitators to patient recruitment (Mason et al 2007). Multiple qualitative methods (including in-depth interviews with RCT participants and recruitment staff, and analysis of information exchanged by recruiters and participants within recruitment appointments) have been used in a trial facing recruitment difficulties with the result of increasing patient acceptance of allocation and randomization rates (Donovan et al 2002, Donovan et al 2008). Early attempts have been made to implement this qualitative package (in the form of a complex intervention) in other trials facing recruitment difficulties, albeit with some challenges, including difficulties establishing collaboration between the qualitative team and RCT staff, poor communication between trial principal investigators and recruiting staff, and recruiters' concerns about having recruitment appointment recorded (de Salis et al 2008, 2008).

Qualitative methods are also increasingly being used within pre-trial feasibility studies, to elucidate and overcome potential process difficulties, and determine appropriate outcome measures, prior to starting the full trial. Such use of qualitative methods was recommended within the Medical Research Council's Framework for evaluating complex interventions (Campbell et al). Yet to date, little attention has been given to the use of qualitative methods at later stages of trials, particularly in relation to the implementation of trial results. This is important as while a trial may produce clinically and statistically significant results, these results may or may not receive recognition or be implemented in the relevant clinical settings. Therefore, the focus of the proposed PhD is to explore how qualitative methods may be incorporated in this post-trial phase to evaluate how trial results are received and implemented, with the ultimate aim of improving the utility of trial results.

Aim

To explore how qualitative methods can be used at the end of randomised controlled trials to evaluate the implementation and utility of trial results.

Methods

- Qualitative case study approach using a mixture of qualitative methods
- Selection of three ongoing/completed trials to act as 'case studies', drawn from trials within COBM or Social Medicine
- Sample of case studies to vary along certain criteria such as: clinical topic, setting in which trial was conducted, setting in which results may be implemented (may be same as trial setting), audience for the results (may overlap with former), fora/journals where results have been published, how 'controversial' the results are.

- Case studies would be staggered, so start with one or two trials that are in the public domain and have another near completed trial as the third case
- Possibilities for data collection:
 - Interviews or focus groups e.g. with clinicians/staff in settings where results are relevant and could potentially be implemented, the trial staff (such as PI, researchers and data analyst); journal editors or reviewers, others
 - Documentary analysis e.g. of responses to publications in journals, trial management group/steering group meeting minutes where dissemination is discussed, written feedback of trial results to various audiences, final reports written by the trial team plus reviewer's comments
 - Observation e.g. observation of end-of-trial management group/steering group meetings where dissemination strategies are discussed, observation of trial feedback meetings where results are disseminated to different audiences (e.g. clinical staff, policy/decision-makers), and leading conferences.

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Supervisor: Dr Alison Heawood, Academic Unit of Primary Health Care.

Secondary supervisor: Prof Jenny Donovan, School of Social & Community Based Medicine

Title: Prevalence and determinants of nonalcoholic fatty liver disease (NAFLD) in adolescence

Outline of project:

The specific objectives of this proposal are:

1. To determine the association of growth trajectories (weight, height and BMI) and changes in waist circumference and fat mass from birth to adolescence and with NAFLD ascertained at age ~17.
2. To determine the association of macronutrients and dietary patterns from birth to childhood with ultrasound scan determined NAFLD and biomarkers for NAFLD ascertained at age ~17.
3. To determine the association of physical activity in childhood with ultrasound scan determined NAFLD and biomarkers of NAFLD ascertained at age ~17.
4. To determine the direction of association between insulin resistance and dyslipidaemia with NAFLD by using the repeat measurements of insulin and lipids at 9, 15 and 17 and determining how these relate to biomarkers for NAFLD assessed at 15 and 17.
5. To examine maternal lifestyle characteristics (including smoking and alcohol consumption) during pregnancy in relation to ultrasound scan determined and biomarkers for NAFLD and to compare these associations with paternal characteristics and the same offspring outcomes.
6. To use genetic variants that are associated with putative causal risk factors for NAFLD to test whether their association is truly causal.

The above objectives 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 NAFLD in adolescence.

Background

NAFLD is characterized by the accumulation of fat in the liver with or without inflammation, fibrosis and cirrhosis, in the absence of substantial alcohol consumption and is considered the hepatic manifestation of the metabolic syndrome¹. There is evidence that NAFLD is increasing in prevalence in adolescents in Europe and other developed countries, and a suggestion that this could have a major impact on future population levels of cirrhosis². Post-mortem studies in the USA suggest a prevalence of NAFLD of 17% in adolescents (aged 15-19) and that the condition is rare before the age of 10³. Our recent work in a general population sample from the USA (NHANES) shows a prevalence of elevated ALT of 8% in 'healthy' adolescents⁴. Amongst adults the longer the duration of NAFLD the greater the likelihood of progression to severe liver disease – fibrosis and cirrhosis, it is therefore likely that individuals with NAFLD in adolescence are at a high risk of severe liver pathology in adulthood if steatosis is not reversed (since by definition having the condition from adolescence into adulthood implies a longer duration than steatosis first appearing in adulthood). However, the current state of art regarding the occurrence and determinants of NAFLD in adolescents is based largely on clinical studies, with relatively small sample sizes and that use cross-sectional or retrospective case control study designs. There is an important need for determining the prevalence of NAFLD in general populations of adolescents in Europe and also for large prospective studies that can determine the key risk factors for NAFLD in adolescents.

Plan of investigations

Analyses will be based on data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population based prospective birth cohort based at the Department of Social Medicine (<http://www.bristol.ac.uk/alspac/>). Data on NAFLD diagnosed by ultrasound (USS) as well as established biomarkers of NAFLD (including ALT, AST, GGT, total bilirubin, fasting glucose, total cholesterol, HDLc, LDLc, triglycerides, apolipoprotein A1 (ApoA1), fasting insulin, alpha 2 macroglobin and haptoglobin), at ages ~15 and ~17 are available as well as all data on potential determinant of NAFLD (anthropometry, diet, etc.). Students will apply appropriate statistical techniques to the specific objectives, including where appropriate multilevel models (e.g. for growth trajectories) and instrumental variables

analyses (e.g. for Mendelian randomization approaches using genetic variants as instrumental variables to establish causality between exposures of interest and NAFLD).

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Supervisors

Prof. Debbie Lawlor & Dr. Abigail Fraser

Title: Factors influencing infant care practices in the sleep environment amongst families at high risk of SIDS

Background

As the number of deaths diagnosed as Sudden Infant Death Syndrome (SIDS) continues to fall the proportion occurring on a shared sleep surface with an adult continue to rise. Around half of SIDS deaths now occur in a co-sleeping environment and this has led some countries (such as the US) to advise against such infant care sleeping practices. The South West Infant Sleep Scene (SWISS) case-control study was conducted from 2003 to 2006 specifically to investigate the sleeping environments in which SIDS infants were found. Our findings suggests it was not so much bed-sharing itself but the hazardous environments in which this occurs that increases the risk of SIDS for such infants [1]. We have also analysed some data from the Avon Longitudinal Study of Parents & Children (ALSPAC) which suggest a complex interdependent relationship between breastfeeding and bed sharing [2]. Before we advise parents in the UK on whether they should sleep with their infants and if so how this may done safely we need to understand some of the factors that influence their decision process on how they sleep, feed and care for their infant, especially amongst parents at higher risk of suffering the tragedy of SIDS. We have available some postal questionnaire data from our SWISS study taken during pregnancy, at birth and at 2,4 and 8 months of age amongst a randomly chosen control group and a control group specifically selected to be at higher risk of SIDS. We also have further longitudinal data available from the larger ALSPAC cohort. Analysis of these data will help drive a contemporary cross-sectional study conducted by the successful candidate of factors influencing infant care practices in a population at higher risk of SIDS and random controls. This will be complemented by a qualitative study of parents which will explore their knowledge and infant care practices in greater detail.

Research questions

The two approaches will try and answer:

1. What factors influence parental decisions on where and how the infant should sleep?
2. Whether there any differences between the high risk and randomly chosen families?
3. To what extent do parental decisions mediate the effect of known SIDS risk factors?
4. How does the mother perceive the relationship between infant feeding and the sleep environment?

Analytical plan

- The student will be expected to complete a systematic literature review of the variation of care practices in the infant sleep environment
- The student under the supervision of a statistician (PB) will analyse the longitudinal data from the SWISS study and supplement this with analysis of the ALSPAC cohort if required.
- A major part of this thesis is to conduct a cross-sectional study of families at high risk of SIDS compared to a randomly chosen control population. The specific questions will mainly stem from the analytical work of the earlier studies but the study design will be decided by the candidate in conjunction with the supervisors. It is envisaged that recruitment will be done during pregnancy with questionnaires collecting quantitative data two to three months after birth. A nested qualitative study will use semi-structured interviews with parents at home to explore in more detail aspects of child care and sleeping practices highlighted in the survey.

The ideal candidate will have a background in observational research, experience in collecting and analysing both quantitative and qualitative data. The student will write up the findings for peer-reviewed publication

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Supervisors: Professor Peter Fleming, Dr Peter Blair, Dr Jenny Ingram

Title: Visual and hearing impairments and unintentional injury in children

Background

Unintentional injury is a leading cause of death for children < 15 years and results in over 2 million hospital attendances per year for this age group, at a cost of at least £146 million per year. The recently published (24/11/2010) NICE guidance on preventing unintentional injuries in children highlights that “there is a lack of epidemiological data on unintentional injuries in the home among under-15s – the types, causes and severity of injuries (in particular, in relation to falls)”. It is known that the risk of unintentional injury is greatest for economically disadvantaged children, but few other risk factors are well described. Children with sensory impairments (hearing or vision loss) are more prevalent in disadvantaged families, but few data are available regarding whether their risk of unintentional injury differs from those of their peers.

This thesis will contribute new evidence to this important topic, using mixed (quantitative and qualitative) methods and a variety of data sources. The outputs will inform policy and practice related to the care of children with hearing or vision impairment, as well as to the current priority area of preventing unintentional injuries in children.

Overall Hypothesis to be tested

Some types of visual/hearing impairment in children are associated with a greater risk of accidental injury in childhood and adolescence

Questions to investigate

Does having impaired vision (VI) or hearing (HI) affect a child’s risk of accidental injury?

If so, are VI/HI risk factors, or protective factors due to modification of child’s environment?

If either true, does this vary by (a) age, (b) setting eg school vs home, or mainstream school vs special school or leisure time vs school-time?

Does risk of unintentional injury vary with type of visual impairment or hearing impairment?

If so – does this inform hypotheses on the causes of accidental injury in children?

Is current advice to parents, carers and teachers of visually impaired/ hearing impaired children optimal as regards injury prevention?

What proportion of childhood accidents are due at least in part, to visual or hearing impairment?

Plan

1. A systematic review of the literature

2. Analysis of existing quantitative data: ALSPAC dataset up to 18 years. Other NHS sources such as hospital data from HES, GP practice datasets. Linked to VI register and/or neonatal hearing screen output

3. Collection of new qualitative data from young people and their parents and teachers.

Advice from YPAG (young people’s advisory group) will be sought so as to include their input on investigations and interpretation of findings.

New data collection:

Interviews with children with visual or hearing impairment of different types

Interviews with teachers, carers, parents of children with VI/HI

Consider the following types of sensory impairment:

Registrable = Severe visual impairment/blindness

Reduced binocularity eg poor stereopsis, suppression

Strabismus

Amblyopia (unilateral)

Visual processing disorders – cvi

Severe/profound sensorineural hearing loss – BSL signers/cochlear implant wearers.

Moderate/severe hearing loss needing hearing aids (unilateral, bilateral)

Early persistent glue ear

4. Combine the results from quantitative analyses and the key themes from qualitative interviews.

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Working base – Centre for Child and Adolescent Health (CAAH), School for Social and Community Medicine

Supervisors – Ms Cathy Williams (Senior Lecturer in Paediatric Ophthalmology, CCAH), Dr Julie Mytton (Consultant in Paediatric Public Health, CCAH) and Dr Amanda Hall (Senior Lecturer, Centre for Child and Balance Studies)

Advisors – Prof Elizabeth Towner, Prof Alan Emond

Title: The Cognitive Neuroscience of Developmental Simultagnosia

Aim : to 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, including 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 quantify 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)

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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 conditions² 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 ALSPAC^{3,4} and to identify the exposures that drive them. Deprivation related to wheezing at 6 months in ALSPAC children⁵ 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 1990/91⁸ (<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)).

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Supervisor

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

Title: Predictors of Persistence and Psychological Impact of childhood Eczema

Eczema is a common problem in childhood, affecting up to 20% of children.¹ Also known as atopic eczema or atopic dermatitis,² the condition is characterized by generalized dry skin, pruritis, and typically flexural erythema. Symptoms usually start before two years of age, and in the UK, most children will be diagnosed and treated by their general practitioner. Whilst the majority of children will have mild symptoms that improve as they get older, a significant proportion of those affected will have more severe and persistent disease. Research suggests that in addition to the physical burden of the condition, eczema in this group may also have a significant psychological impact on the child and their family.

The condition appears to have a strong genetic basis, with a lot of interest recently focused on defects in a gene that encodes for a structural protein in the skin called filaggrin.³ However, environmental factors are still thought to play an important role, some of which may be modifiable. This study is therefore concerned with identifying characteristics of children with eczema and their families which predict persistent eczema, and quantifying the psychological impact of persistent eczema on them. This will help in the development of interventions to reduce the physical and psychological burden of the disease.

Studies of the natural history of eczema and factors that predict persistence

Our knowledge about the natural history of eczema and factors that might predict persistence beyond the pre-school years is limited by the methodological imperfections of research conducted to date. Most studies have either been small, retrospective case series, suffered from a short duration of follow-up or recruited participants from hospital in or out-patients.⁴ As a consequence the findings may be unrepresentative of children in the community and subject to the many biases that are associated with a retrospective study design. The most robust investigations have been undertaken by Williams and Strachan⁵ and Illi et al.⁵

Williams and Strachan⁵ used the National Child Development Study (NCDS), which is a birth cohort of British children born in one week in 1958. Of the 571 children with eczema by the age of 7 years, 198 children (35%) and 150 children (26%) were reported to still have eczema at 11 and 16 years respectively. Compared with previous hospital-based studies, the onset of the disease in this population appeared to be later yet earlier onset of eczema was associated with more persistent disease. This vindicates the concern that studies of eczema cases based on hospital series are more likely to include more severe cases, because earlier disease onset appears to be a determinant of prognosis and troublesome cases are more likely to be referred to hospital. However, this was primarily a study which described the natural history of eczema rather than an investigation of predictors of persistence *per se* and data on the presence/absence of eczema were only collected at four time points (ages 7, 11, 16 and 23 years). The inception cohort was defined as all those children with examined or reported eczema by the age of 7 years (n=571), with the authors having to rely on parental recall for the presence of eczema during the first year of life. The absence of data for ages 8-10 years, for example, means recurrences occurring in these periods would have resulted in more unfavourable prognosis for long-term clearance rates.

Illi *et al*⁵ used data from a German birth cohort (the Multicenter Allergy Study, MAS) to examine the natural course of eczema and prognostic factors. MAS recruited 1314 of 7609 children born in five cities in 1990 and followed them up at the age of 1, 3, 6, 12, 18, and 24 months and thereafter yearly up to the age of 7 years. In total, 1123 MAS children were included in the analysis and the cumulative prevalence of eczema in the first 2 years of life was 21.5%. Of these children with early eczema, 43.2% were in complete remission by age 3 years, 38.3% had an intermittent pattern of disease, and 18.7% had symptoms of AD every year. Determinants of prognosis were severity, atopic sensitization and a strong atopic family history (defined as two or more atopic family members).

The psychological impact of eczema

Nearly all studies that describe the psychological effects of atopic eczema on children and their families/carers have serious limitations, related to either sample size, reference population (mainly hospital out-patients), study design (most are cross-sectional) and/or the primary outcome measure used (the majority examine the psychological effect of eczema on the child only).¹ Only one recently published study, by Schmitt *et al*,⁶ followed-up a sizeable cohort of children for a reasonable length of time.

Schmitt *et al*⁶ analysed data on 2916 children from the German Infant Nutrition Intervention plus (GINIplus) birth cohort. Eczema was defined on patient report and psychological outcomes were assessed using the German version of the Strengths and Difficulties Questionnaire (SDQ). Compared with participants never diagnosed as having eczema, children with infant-onset eczema had a significantly increased risk for emotional symptoms (odds ratio 1.62, 95% CI 1.25-2.09), and the strength of the association between eczema and emotional problems increased with increasing eczema persistence. However, the SDQ was only administered once, at 10 years of age, and no psychological measures were administered to the parents.

The ALSPAC cohort and previous studies of eczema

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth cohort study based in Bristol. It is described in more detail elsewhere,⁷ but briefly it recruited more than 14,000 pregnant women with estimated dates of delivery between April 1991 and December 1992. These women, the children arising from the index pregnancy and the women's partners have been regularly followed up since.

Data collected as part of the ALSPAC cohort on eczema remains largely unexplored, with four published studies that have focused on the epidemiological and clinical aspects of the disease,⁸⁻¹¹ all limited to the preschool period. There have been no studies that have looked for associations between persistence of eczema and the various measures of child and parental psychological health routinely collected. This project will both build on the previous studies that have used ALSPAC data and address the limitations of the other research to examine the relationship between factors that predict persistence of eczema and its psychological consequences.

Supervisor(s)

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

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Title: Preventable emergency hospital admissions in children: exploring parental and professional perceptions and identifying potential interventions

Background

Admissions to hospital place an increasing burden on health care resources. Unplanned admissions to hospital represent 36.7% of hospital admissions in the UK (4,659,054 emergency admissions in 2005/6). Short stay unplanned hospital admission rates in young children in England have increased substantially in recent years. The majority are for minor illness episodes that could be managed by primary care in the community.

Aim

1. To explore decision making by parents/carers around health service use when faced with an unwell child
2. To explore health care professionals view of appropriate management for young children with conditions that commonly result in admission
3. To understand the perceptions and values that underpin these views and decisions
4. To develop and pilot an intervention aimed at parents/carers of young children with a view to reducing preventable hospital admission

Plan of investigation

Commencing with a literature review, the research project will use a combination of qualitative and quantitative methods. Participating parents/carers will be recruited to a qualitative interview study to explore why a potentially preventable hospital admission occurred in the case of their child. The perceptions and values underpinning the decisions made will be explored in depth through semi-structured interviews that will be audio-recorded and transcribed verbatim. The interview data will be analysed thematically, with coding and organisation of the data aided by the software ATLAS.ti. Health care professionals will be invited to contribute, through a group-based consensus building method such as the Delphi technique, to the development of plans for interventions to help parents to access appropriate and timely care for unwell children. Routinely available health care data will be analysed using quantitative techniques and statistical software (STATA) to describe the burden of admissions in the local health care community and associated risk factors and to identify possible target conditions for an intervention.

Using a synthesis of the data from the literature review, parental and professional sources and routinely available admission data, an intervention aimed at reducing emergency admissions for a target subgroup of patients with a common cause of preventable admission will be developed and piloted for acceptability and feasibility.

Impact

Current policy and planning for reducing hospital admission is often 'top down' with central directives and local budgetary considerations driving the implementation of clinical guidance. This work will identify how parents and professionals perceive decisions around preventable admissions in young children and will lead to an intervention that can be utilised in the NHS.

Supervisor: Dr Sarah Purdy, Academic Unit of Primary Health Care

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

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 Department 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 Professor Ricardo Araya

Title: Understanding HPA axis dysfunction in severe treatment resistant depression

Project Outline

The discovery of abnormal HPA axis function in depression in the 1970s led to the development of two main tests for documenting it: the dexamethasone suppression test (DST) and the combined corticotrophin releasing factor/dexamethasone suppression test (CRF/DST). These were developed in the hope that they would be biomarkers for particular forms of depression, aiding treatment selection and drug development. However they are not specific enough to be useful (also abnormal in schizophrenia, dementias, neuroses etc) and are affected by many extraneous factors. Nevertheless, the evidence produced suggests that people who have treatment resistant depression (TRD) are very likely to have HPA axis abnormalities and that recovery from an episode of illness is often associated with a recovery of HPA homeostasis. This makes the HPA axis a system worth probing in more detail, as an interesting potential therapeutic target, and an area of special interest to develop biomarkers that may have predictive value. Professor Lightman is a world leader in understanding of HPA axis pulsatility and feedback and his group's discoveries in the field of human physiology can also be applied to gain a more sophisticated understanding of neuroendocrine imbalance in TRD.

This PhD focuses on developing some of the following tests (which we have used in Bristol in healthy volunteers studies) to increase our understanding of the HPA dysfunction in TRD.

1. Inhalation of 35% CO₂ which produces an increase in cortisol and ACTH. In addition it also has effects on 3 other dimensions (sympathetic, parasympathetic and psychological) that generate added value in the interpretation of data. This provides a robust assessment of HPA axis reactivity.
2. The administration of high dose hydrocortisone in a MRI scanner which produces decreases in ASL signal in areas germane to HPA control such as the hippocampi, hypothalamus, and networks that process emotion in fronto-striato-thalamic loops. These changes reflect a change in neuronal firing in these areas. This provides an assessment of brain reactivity to glucocorticoid receptor stimulation.
3. Ultradian pattern of 24 hour cortisol secretion and polysomnography. This provides an index of cortisol pulsatility, of overall secretion and of their relationship to objective sleep measures.
4. Exogenous corticosteroid modulation of ultradian pulsatility

In patients with TRD there are two possible outcomes:

- a) patients have the same responses as healthy volunteers. This implies that these tests are not affected by the baseline changes and will be useful in determining dose range, brain penetration and efficacy of novel HPA modulators in patient samples
- patients have different responses compared with healthy volunteers in which case these tests will have the potential to provide surrogate end points.

Supervisors: Dr A L Malizia, Dr S J Wilson, Professor S Lightman

Title: Opiates, pain and sleep

Project Outline

The relationship between pain and sleep is a complex one. On one hand complaints of fragmented or unsatisfactory sleep are very common in patients with chronic pain, and on the other there is evidence that sleep problems may cause hyperalgesia, while sleep itself has an antinociceptive effect. The association between pain and sleep problems has also become evident in populations not identified as suffering from chronic pain, but with chronic medical illnesses generally. Insomnia, often long-lasting, is also common in people withdrawn from opiates such as methadone, as are complaints of pain.

This project will investigate the links between pain, sleep and quality of life in 3 groups of people: - 1. opiate addicts maintained on methadone or buprenorphine or detoxifying from these drugs; 2. patients attending a chronic pain clinic; 3. patients referred for deep brain stimulation for the relief of severe chronic pain. Methods will include qualitative research, questionnaires and objective sleep recording. In addition, repeating the investigations after institution of deep brain stimulation in group 3 will give information about the how sleep changes with pain severity.

This study will provide essential information about the role of sleep in these situations, so that the importance of treating sleep complaints may be assessed. The two supervisors bring complementary expertise to the area. Dr Wilson is a renowned sleep expert, who has conducted and supervised many similar studies in the Psychopharmacology Unit since the early 1990s, whilst Dr Melichar is a Clinical Senior Lecturer in the Psychopharmacology of Substance Misuse, is medical lead of the Bristol NHS substance misuse service and runs the joint substance misuse/chronic pain service with Dr Cathy Stannard.

Supervisors: Dr J K Melichar, Dr S J Wilson

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 depression¹. Approximately 25-40% of adolescents exhibit high levels of depressed mood². 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 behaviour³. 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 adolescence⁴⁻⁶. Although underlying temperament traits may be associated with vulnerability for internalizing problems, other factors must co-occur for depression to develop⁴. This is consistent with a vulnerability / stress-diathesis model, with underlying temperament as the diathesis⁷.

From the perspective of a vulnerability model, a vulnerable temperament must be accompanied by adversity for depression to develop⁸. Prior research has found a strong association between emotional symptoms and parent-child relationships⁹⁻¹², and this relationship is modified by the child's temperament¹³. 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 adolescence¹⁴⁻¹⁶. However, there are methodological limitations to previous studies including relatively small sample size and cross-sectional design³. 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 adolescence¹⁷⁻¹⁹.

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 SDQ²⁰ and DAWBA²²) in the association between temperament and depressive symptoms.

Supervisors: Dr. Carol Joinson, Professor Ricardo Araya.

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

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: Digit ratio, development, gender orientation and disease.

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 literatureⁱ. 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 QIMR 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.