Tuesday 9 August 2011
Parallel session 3
3.1 NOVEL APPROACHES TO REDUCING BIAS

Chair: Prof. Iain Crombie, UK

03-1.1 DOES DROP-OUT FROM COHORT STUDIES BIAS ESTIMATES OF SOCIOECONOMIC INEQUALITIES IN HEALTH?

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Introduction Scandinavian studies exploiting record-linkage have shown that although cohort members tend to be healthy and affluent compared to the whole population, this does not bias at least certain well-established exposure-outcome associations. It is unknown whether this holds when estimating health inequalities. Individuals of lower socioeconomic position (SEP) may be less likely to consent to participation in a cohort study and more likely to drop-out over time.
Methods We assess whether socially-patterned drop-out affects the estimation of health inequalities in the Avon Longitudinal Study of Parents and Children. In this UK cohort, children of higher SEP (measured by maternal education) are more likely to continue participating as they get older. We estimate SEP inequalities in maternal and infant outcomes for which we have data on almost the whole cohort (birthweight and length, breastfeeding, preterm birth, maternal obesity and smoking during pregnancy, N ~ 12 000). We then restrict analyses to individuals who participated in subsequent data collections when the child was aged 9 (N ~ 7000) and aged 15 (N ~ 5000).
Results Drop-out was related to SEP and outcomes, so under missing data theory analysis may be biased. For each outcome, inequality was greatest in the full sample; the more selected the sample became, the more the inequality was underestimated; for example, mean birthweight difference between highest and lowest SEP was 116 g (95% CI 78 to 153) in the full sample, but 93 g (95% CI 45 to 141) and 62 g (95% CI 5 to 119) in those attending at ages 9 and 15 respectively.
Conclusion Selection bias in cohorts may result in underestimation of health inequalities.

03-1.2 HOW TO PERFORM A SENSITIVITY ANALYSIS EXPLORING THE IMPACT OF MISSING NOT AT RANDOM DATA WITH THE R® SOFTWARE

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Introduction The impact of missing data (MD) on the validity of results, although often discussed, is not often investigated. Sensitivity analyses under different scenarios of non-ignorable MD are an attractive approach but they are rarely performed, probably due to lack of tools.
Methods We propose an R function to perform multiple imputation based on the principle of mixture modelling, assuming that the variable of interest has different distributions according to the status missing / non-missing. We propose a 3-step strategy:

Fit an imputation model assuming ignorable MD;

Modify the imputation model by adding a parameter (expressed as the OR comparing the odds of the modality of interest among subjects with MD with those without MD for categorical variables; as the difference in expected values for continuous variables);

Impute MD under the scenario thus specified.

A sensitivity analysis was performed on data from HIV+ patients, to assess the robustness of the OR between mental health and self-reported viral load, including MD. We assumed that non-responders were more likely to have high viral load.
Results Adjusted OR was reduced from 2.01 [1.21 to 3.35] to 1.75 [1.03 to 2.97]. Conclusions were robust to the explored scenarios reinforcing the confidence in results from the analysis assuming ignorable MD.
Conclusion A sensitivity analysis is easy to perform using the proposed package SensMice. The impact of imposed variations in the imputation model on the overall results helps to assess their robustness. This is particularly interesting for self-reported characteristics when MD are highly suspected to be non-ignorable.

03-1.3 SENSITIVITY ANALYSIS FOR AN APPARENT DIRECT EFFECT AFTER CONDITIONING ON AN INTERMEDIATE VARIABLE

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Introduction Determining factors in the causal pathway between an exposure and a disease is often the aim of etiologic research. For example, if a gene is associated with a certain disease, one would like to know if this relation can be explained by one or more intermediary variables. A naive approach to explore this is to condition on the intermediate factor and perform a stratified analysis. However, when an association remains, it is not always clear how this should be interpreted. It may be explained by a true direct effect of the exposure on the disease, or it may be explained by different types of error.
Methods We study different situations, using directed acyclic graphs, where despite absence of a direct effect, still a conditional relation between the exposure and the outcome remains. By quantifying the effect on the association parameter in each of the situations, we develop tools for sensitivity analysis of the completeness of adjusting for a mediator. The performance of the sensitivity tools is studied by simulation and by applying the tools on data of the LETS study. In this case-control study the question was whether the relation between blood group and venous thrombosis was mediated through coagulation factor VIII.
Results A remaining association can be caused by different types of measurement error, reverse causation or unmeasured confounding. In the LETS study intra-individual variation explained most of the remaining association.
Conclusion Sensitivity analyses should be performed before the conclusion is made that effects are not completely mediated.

03-1.4 MULTIPLE IMPUTATION: PANACEA OR PLACEBO, THE CASE OF MISSING CAROTID INTIMA-MEDIA THICKNESS MEASUREMENTS IN CLINICAL TRIALS

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Introduction We assessed the added value of multiple imputation (MI) of missing values in longitudinal datasets with carotid intima-

media thickness (CIMT) as primary endpoint subsequently analysed with linear mixed effects (LME) models.

Methods Analyses were based on a subset of 300 participants from the METEOR (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin) trial. CIMT measurements were performed at 12 carotid sites over seven examinations. The "true" difference in rate of change in CIMT between rosuvastatin and placebo was derived from a completed dataset. Scenarios with missing values were defined, both MCAR (Missing Completely At Random) and MAR (Missing at Random), with 10 to 60% missing values, related to, among others, age and treatment allocation. LME analyses were performed with and without preceding MI. The added value of MI was assessed by comparing the LME estimates with the true value in terms of bias and precision.

Results Bias in point estimates for LME analysis with and without preceding MI was similar in scenarios with ≤40% missings. With 60% missing values, LME without MI was superior to LME with MI. Coverage of the 95% CIs was similar for LME with and without MI for all scenarios.

Conclusion Applying MI prior to LME analyses on longitudinal CIMT measurements does not increase precision or reduce bias in the estimated differences in rates of change in CIMT. Hence, MI has no added value in this context, and direct application of LME remains the preferred method in trials using CIMT as primary endpoint.

03-1.5 USING DATA LINKAGE TO EXPLORE USE OF GP SERVICES BY SMOKERS

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Introduction It is understood how confounding of mediator-outcome associations resulting in collider biases may cause error when estimating direct and indirect effects. Here we assess the impact of non-differential and independent measurement error of the exposure and mediator.

Methods We used as a motivating example the association of childhood socioeconomic position (exposure) with adult psychological distress (outcome), and possible mediation by adult socioeconomic position (mediator). We use quantitative bias analysis methods to quantify the impact of misclassification of exposure and mediator on three target parameters: the total effect of exposure on outcome; the direct effect (by conditioning on the mediator); and the indirect effect (identified by the percentage reduction in the excess OR upon adjusting for the mediator).

Results ORs before and after adjustment for mediators are both biased to the null by non-differential misclassification of the exposure, but the percentage reduction in the excess OR is not affected by measurement error of the exposure. Conversely, measurement error of the mediator rapidly biases the percentage reduction the excess OR downwards.

Conclusions If the research objective is to quantify the proportion of the total association that is due to mediation (ie, indirect effect), then minimising (or adjusting for) non-differential misclassification bias of the mediator is much more important than that for the exposure (or outcome). Considering the relative importance of collider bias and measurement error when estimating direct and indirect effects, measurement error (of mediators in particular) will often be a (much) greater source of systematic error.

03-1.6 SYSTEMATIC REVIEW OF RECORD LINKAGE STUDIES OF MORTALITY IN EX-PRISONERS: WHY GOOD METHODS MATTER

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Introduction Worldwide more than 30 million people move through prisons each year. Record linkage studies have identified a markedly increased risk of death in ex-prisoners. In order to inform preventive interventions it is first necessary to understand who is most at risk, when and why. Unfortunately, limitations of existing studies have rendered synthesis and interpretation of this literature problematic.

Methods Systematic review of studies using record linkage to explore mortality in ex-prisoners. Based on analysis of >20 studies, we illustrate how methodological limitations and heterogeneity of design, analysis and reporting both hamper data synthesis and create potential for misinterpretation of findings. Using data from a recent Australian study involving 42 015 ex-prisoners and 2329 observed deaths, we quantify the variation in findings associated with various approaches.

Results For example, given the very different age distributions of prisoners and the general population, the all-cause SMR among the cohort was 1.4 (95% CI 1.4 to 1.5) using direct methods and 3.1 (95% CI 3.0 to 3.2) using indirect methods. When the period of observation was constrained to 12 months from any release, the indirect SMR increased to 5.3 (95% CI 4.9 to 5.7). Similarly, when analyses were based on the first occasion of release during the period of observation the CMR was 9.3 (95% CI 8.4 to 10.3) per 1000 py, whereas based on the most recent release the CMR rose to 16.9 (95% CI 15.6 to 18.2) per 1000 py.

Conclusion We conclude with a series of recommendations for future studies, and provide a checklist for optimising study design, analysis and reporting.