NEW ADVANCES IN EPIDEMIOLOGICAL METHODS
PLENARY I

001 Statistical methods for exposure-response modeling

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Exposure-response modeling in occupational epidemiology is usually motivated by questions of causal inference (is there a monotonic increase of risk with increasing exposure?) or risk assessment (how much excess risk exists at any given level of exposure?). Here we focus on statistical models for exposure-response in mortality studies. Categorical analyses are useful for detecting the shape of exposure-response, but are dependent on cutpoints and are less useful for risk assessment which requires a parametric curve. Restricted cubic splines and penalized splines are useful intermediates between categorical and simpler parametric curves, may help to choose a simpler parametric curve. The shapes of spline curves will depend on the degree of "smoothing" chosen by the analyst. Exposure-response curves in occupational epidemiology often flatten out at high exposures, for a number of reasons (eg., greater misclassification at high exposure, saturation of metabolic pathways, etc). A log transformation of exposure often provides a good parametric fit to such curves, but has the disadvantage of a very high slope at low exposures, which may be the relevant exposures for environmental risk assessment. A piece-wise linear model may be a useful alternative. In general, the model with the best statistical fit may not be the "best" model for risk assessment. Another model of interest is a threshold model in which there is no risk before a certain threshold. Finally, Bayesian restrictions on exposure-response curves may prove useful in some settings in increasing precision. These points are illustrated using data from several epidemiologic studies.

002 Evaluation of the shape of exposure-response relationships for high molecular weight sensitizers: implications for risk assessment

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Background. In recent years, exposure response relationships have been published for several high molecular weight sensitizers (fungal a-amylase, wheat allergens, rat urinary proteins). Little is known about the shape of the exposure response relationship, because available exposure data have not always been used in the most informative way. More information about the shape of the relationship is useful because it allows evaluation of the presence of an exposure threshold and results can be used as input for risk assessment purposes. Recently, studies with domestic allergens suggested that the exposure response relationship might be bell shaped, possibly due to tolerance associated with development of IgG4 antibodies at higher exposure levels. We explored the shape of exposure response relationships for three different allergens (fungal a-amylase, wheat allergens and rat urinary proteins) studied earlier in four independent cross-sectional studies with 350 to 600 workers in each study.
Methods. In each study more than 500 air allergen exposure measurements were available to characterize the exposure with job exposure matrices by job, industry and, if appropriate, task level. Information on specific work related sensitisation was available (skin prick test response or specific IgE) as well as atopic and symptom status. Semi-parametric GAM modelling, with exposure as additive predictor, fitted by a spline smoother, was applied to evaluate the shape of the exposure response relationship. This approach was used to see whether parametric models could be fitted to describe exposure sensitisation relationships in a more straightforward way.
Results. For all allergens steep exposure response relationships were found in the low exposure range, with large increases in sensitisation risk per unit of exposure. Relationships were usually steeper for atopics. No evidence for the existence of exposure thresholds existed. The shape of the exposure response relationships differed from simple increasing risk curves to bell shaped relationships described either by simple and quadratic logistic models.
Conclusions. No evidence for the presence of exposure thresholds was seen for any of the allergens indicating that complete elimination of a sensitisation risk does not seem possible. Alternatively, benchmark approaches are needed to estimate the risk at certain exposure levels. Reasons for lower sensitisation risk at higher exposure levels need to be explored, development of tolerance or its presence might play a role, but the fact that different relationships were found for the same allergen (wheat) in two independent population studies suggests that other factors might be a more plausible explanation.

003 Adjusting for dependent censoring, survivor biases and intermediate confounders: a cohort study on lung cancer risk in German coalminers

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Background. Standard analyses of epidemiological studies are potentially distorted by dependent censoring due to competing risks, intermediate confounders and survivor biases. Lung cancer risk after quartz dust exposure or coalmine dust exposure is a typical example with radiographical fibrosis being a potential intermediate confounder. We used g-estimation (Robins 1998) to tackle these structural problems in an analysis of a German follow-up study on coalminers' lung cancer risk.
Methods. A mortality follow-up was conducted on 4581 coalminers from 1980 through 1998. More than 30.000 gravimetric dust samples were used to calculate time-dependent personal exposures to respirable coalmine dust and quartz dust. Additional tyndalloscopic intensity values were converted into gravimetric units on the bases of 1.682 comparison measurements. About 100.000 radiographs were re-evaluated according to ILO 1980 to describe the pneumoconiosis process. A sparse sample of 24 measurements was available for a very crude estimate of radon exposure. We could extract smoking data for 2.415 coalminers (active, ex, never smoker; duration; intensity; pack-years). SMR-analyses, Cox-modelling and g-estimation was performed. For the latter a specific causal accelerated failure time model was chosen. Causal parameters were estimated by a sequence of inverted longitudinal GEE-regression models adjusting for 26 covariates. The inverse of the probabilities of competing risks (estimated by logistic regression with time-dependent covariates) were used as weights in the estimation process to correct for dependent censoring.
Results. 98 lung cancer deaths occurred (SMR=0.79, $p<0.05$). A Cox-model with 8 covariates came up with a coefficient for ILO ≥1/1 (yes/no) of 1.08 ($p=0.0001$), for quartz dust exposure in mg/m³ x shifts of -0.119 ($p=0.01$) and for non-quartz dust exposure in mg/m³ x shifts of 0.04 ($p=0.12$), all time-dependent. G-estimation showed a significant impact of the ILO-process on lung cancer risk but could not find an overall effect of dust exposures.
Conclusion. An excess of lung cancer risk in pneumoconiotics demonstrated by internal analyses appears to be linked to the fibrosis process only. The method of g-estimation appears to be a powerful tool to analyse occupational epidemiology studies in a causal manner by taking the complex longitudinal structure of occupational health more appropriately into account than conventional approaches.

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