

measured by intermediate markers into the modelling of the natural history of cancer. Together with its ability to elucidate temporal effects of exposure on disease risk, this suggests a large range of applications in chronic disease epidemiology.

## Session: 20. Risk modelling

### 328 MODELLING COMPLEX MIXTURES IN EPIDEMIOLOGIC ANALYSIS: ADDITIVE VERSUS RELATIVE MEASURES FOR DIFFERENTIAL EFFECTIVENESS

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Mixed exposures are often combined into single exposure measures using weighting factors. An example of this arises in radiation epidemiology where doses of distinct forms of ionising radiation (such as alpha, beta, and gamma radiation) are combined based on knowledge of their biological effectiveness relative a reference form of radiation (most often gamma). Similar pooling of mixed exposures may occur with multiple congeners or air pollutants to develop more parsimonious models. The weights used for combining exposures are determined from experimental animal and cellular research, but not observational research. In this work, we show that these weights, which are the ratio of two normally distributed variables, cannot be reliably estimated from observational research. We propose an alternative approach for estimating differences in effectiveness of distinct exposures based on their excess effectiveness compared to a reference exposure. This alternative provides reliable estimates of differences in effectiveness of distinct exposures.

### 329 IMPROVING COUNTER-MATCHING DESIGN IN NESTED CASE-CONTROL STUDY TO ANALYSE THE EFFECT OF A CONTINUOUS OCCUPATIONAL EXPOSURE

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**Introduction** Nested case-control studies are classically used in epidemiology to reduce time and cost for data collection while minimising bias induced by sample size reduction. However, if the continuous exposure of interest have a highly skewed probability distribution, rare exposure values are less likely to be selected. Therefore, the sampling process can miss important information in the long tail of the exposure distribution. Counter-matching design attempt to maximise the information on known exposure of interest during sampling process by the selection of controls in several categories covering all the range of the exposure. This study attempt to assess the influence of the choice of the categorisation method on the risk estimation.

**Method** The categorisation of continuous exposure is provided by several classification or clustering Methods: a priori thresholds, quantiles and k-means. To investigate the robustness of these methods, a simulation study is realised with several shapes

of the probability distribution of the exposure, addition of covariate and missing collected data. Theoretical results will be illustrated with the example of a case-control study of cardiovascular diseases mortality (440 cases, 5 controls per cases (1:5)) nested within the French cohort of uranium miners (including 5086 men followed-up between 1945 and 2007) where cases and controls are matched on age and birth cohort and counter-matched on cumulative radon exposure.

**Results** 5000 samples 1:5 have been generated from the French uranium miners cohort for each methods applied on the cumulated radiation exposure. Relatively to the risk estimated from the cohort, the bias was systematically lower by using the k-means method.

**Perspectives** Results of the simulation study and application to the case-control study nested within the French uranium miners cohort could confirm this trend and contribute to the improvement of the efficiency of nested case-control study for the assessment of risk of exposure.

### 330 A DYNAMIC POPULATION-BASED MODEL FOR THE DEVELOPMENT OF WORK-RELATED RESPIRATORY HEALTH EFFECTS AMONG MOTOR VEHICLE REPAIR WORKERS EXPOSED TO ISOCYANATES

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**Objectives** Spray painters, who are exposed to isocyanate mixtures, are among the occupational groups with the highest incidence of occupational asthma in industrialised countries. In the Netherlands the motor vehicle repair (MVR) industry comprises one of the largest occupational populations potentially exposed to isocyanates. We present a mathematical model which simulates a population of spray painters exposed to isocyanates longitudinally through time and tracks the development of symptoms in each worker.

**Methods** First, based on the literature a conceptual disease model was defined which differentiates between different severities of symptoms: healthy, upper airway symptoms only, lower airway symptoms only, both upper and lower airway symptoms, and work-disabling symptoms, where all states are stratified on sensitisation. A Weibull survival analysis of data from an epidemiological study of 424 workers in the Dutch MVR industry confirmed the relationships of respiratory symptoms with isocyanate exposure and atopy. Furthermore, the data provided us with the necessary task-based exposure distributions, patterns of work and use of respiratory equipment that served as inputs for the simulation model.

**Results** Individual workers had the highest chance of developing respiratory symptoms within the first five years of working in the MVR sector, after which their risks decrease. Furthermore, the risk of developing lower airway symptoms after 5 years doubled when a worker was atopic. The following example illustrates the application of the modelling approach: The prevalence of lower airway symptoms found in the epidemiological study was 5%. On average, 93% of spray painters used respiratory protection equipment. The dynamic population model predicted that when frequency of use increases to 98%, the prevalence of lower airway symptoms would decrease to 4%.

**Conclusions** The presented simulation model may be used to evaluate the change in health outcomes that result from different intervention strategies for the MVR sector.

### 331 A DYNAMIC POPULATION-BASED MODEL FOR THE DEVELOPMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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**Objectives** We present a mathematical model for the development of chronic obstructive pulmonary disease (COPD), incorporating population dynamics, trends in smoking, and occupational exposure to respirable dust, fumes and gases. The model simulates a population of workers longitudinally throughout their lifetimes and allows us to study the combined effects of smoking and exposure on the development and progression of COPD.

**Methods** The model comprises: a population model, describing the attributes and dynamics of the population; a smoking model, representing demographic and individual trends in smoking; an exposure component, characterising inter- and intra-individual variation and temporal trends in occupational exposures; and a disease component, describing changes in FEV1, FVC, symptoms and exacerbations. Lung function parameters associated with a “healthy” population were estimated from international health surveys. Annual mean excess declines in FEV1 relating to smoking and occupational exposure to several agents, including coal dust and silica, were sourced from literature. Inter-individual variation in declines encapsulates susceptibility of individuals, some of whom will experience especially deleterious effects of smoking and exposure. Sensitivity analysis provides information on the most influential parameters and uncertainties associated with the model.

**Results** A preliminary simulation without occupational exposure predicted a current prevalence of >10% in males of working age, consistent with a recent Health Survey for England study, and a modest decline over the next 30 years due to recent trends in smoking participation rates. Using coal dust as a surrogate for poorly soluble dusts, the model confirms that reduction in long-term exposure decreases an individual’s risk of developing COPD, with the greatest impact in non-smokers.

**Conclusions** The model provides us with valuable information on current and future trends in COPD in Britain. It may be used to assess the effects of reducing levels of exposure or of introducing health surveillance.

### 332 DURATION AS A PROXY FOR CUMULATIVE EXPOSURE: SHOULD WE TRUST POSITIVE RESULTS?

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**Objectives** We considered a problem common to occupational epidemiology, where cumulative exposure is the true dose metric for disease but investigators are only able to measure duration of exposure.

**Methods and Results** We considered the problem from the theoretical perspective and explored our results in simulations of an occupational cohort of medium size. The duration of exposure is related to cumulative exposure by measurement error with some properties of Berkson-type error. This arises because cumulative exposure = duration\*intensity and can be re-written as true = observed\*error, with error term having distribution of average long-term exposure intensity for a worker. When duration and intensity are independent, the theory predicts that fitting duration instead of cumulative exposure will not inflate probability of type-I error under the null hypothesis. However, when there is an association between cumulative exposure and the outcome, loss of power to detect an association is expected. In practice, data do not always conform to assumptions made in the theoretical study. We confirmed these predictions in a simulation study for a cohort of 1000 workers with rare outcome in unexposed and with varying correlation of intensity and duration. We first analysed the data using logistic regression models including metrics of exposure as continuous variables. We then explored the situation where exposure groups are formed using quartiles of observed exposure metrics among “cases” and odds in the highest quartile are compared to the lowest. Patterns observed in both analyses were consistent with those expected from theory.

**Conclusions** Epidemiologists should be more confident in interpreting positive results that arise from use of duration of exposure in lieu of true dose metrics when it is cumulative exposure because type-I error remains at nominal values. The interpretation of null associations remains difficult due to loss of power.

### 333 ADAPTING AN INTERRUPTED TIME SERIES DESIGN TO VOLUNTARILY REPORTED SURVEILLANCE DATA: ADVANTAGES OF STATISTICAL INTERACTIONS IN REDUCING BIAS

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**Objectives** To describe the method we use to identify temporal associations between events such as changes in legislation and changes in the incidence of work-related ill-health (WRI) using surveillance data and to show some examples applying this method.

**Methods** The Health and occupation reporting network (THOR) collects reports of work-related ill-health from clinical specialists. Previously we have published a method to analyse time trends in the incidence of WRI using a 2 level negative binomial regression model with beta distributed random effects<sup>1</sup>. The model also controls for calendar time, reporter type (monthly or annual reporter) and first month as a new reporter. One variable that influences reporting to the THOR surveillance scheme is the length of membership time *i.e.* reporters tend to report fewer cases after longer membership time resulting in an inherent downward trend in incidence. In an attempt to mitigate this effect, alongside other factors affecting trends in reporting that are not directly related to the incidence of WRI, we have employed a segmented interrupted time series design and included statistical interaction terms in the model. Briefly time periods describing the time periods pre and post-event, and groups representing cases and comparators are prospectively defined. Groups are usually defined by occupation and/or suspected agent. Comparisons are made of the estimated change in incidence per reporter according to inclusion or exclusion within a group.