

Objectives Standard data analysis procedures provide biased answers to etiologic questions in occupational studies. G-estimation is an alternative that allows researchers to avoid healthy worker survivor bias, and its results can be expressed as estimates of the impacts of hypothetical policy interventions.

Method Rather than estimating the association between observed exposure and observed outcome, g-estimation models the counterfactual outcomes under no exposure as a function of observed outcomes and exposures. Adjustment for confounders is achieved by predicting exposure conditional on those confounders and on the counterfactual outcome. The method leverages the assumption that all confounders are measured: within strata of the measured confounders, observed exposure is “randomised”—that is, statistically independent of counterfactual outcome. This allows for correct adjustment for time-varying confounders affected by prior exposure and thus avoids healthy worker survivor bias.

Results Results can be expressed in terms of the impacts of hypothetical exposure limits. For example, after g-estimation of an accelerated failure time model, counterfactual survival times under a series of specified exposure limits can each be compared to observed survival time. This allows the researcher to report estimates of the total number of years of life that could have been saved by enforcing each limit.

Conclusions G-estimation is a valuable tool for occupational epidemiologists because it can both prevent bias due to the healthy worker survivor effect and estimate the impacts of hypothetical exposure limits.

0359 NIGHSIFT WORK AND BREAST CANCER RISK – GOOD NEWS, BAD NEWS?

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Objectives Using two large prospective data sets, we explored associations between rotating nightshift work and breast cancer risk.

Method Among 193 396 women from the Nurses’ Health Study (NHS and NHS2) cohorts, we documented 5575 (NHS) and 2869 (NHS2) incident invasive breast cancer cases as well as 696 (NHS) breast cancer deaths over 22 years of follow-up. Compared to our initial analysis within NHS, which was based only on 10 years of follow-up and showed that 30+ years of rotating nightshift work was associated with a 36% significant increase in breast cancer risk, we added 12 years of follow-up, which were accrued for the most part after nurses’ retirement.

Results In these extended analyses, 30+ years of rotating night shift work was no longer associated with breast cancer risk (multivariable $RR_{30+ yrs} = 0.95$, 95% CI 0.77–1.17; $p_{trend} = 0.95$), and only insignificantly associated with breast cancer mortality (multivariable $HR_{30+ yrs} = 1.50$, 95% CI, 0.95–2.36). By contrast, in the younger NHS2 cohort, baseline 20+ years of rotating nightshift work was associated with a significantly increased risk of breast cancer ($RR_{20+ yrs} = 2.11$, 95% CI 1.21–3.66; $p_{trend} = 0.22$). Updated rotating night shift work exposure was also associated, albeit non-significantly, with a modest increase in risk of breast cancer ($RR_{20+ yrs} = 1.33$, 95% CI 0.93–1.89; $p_{trend} = 0.68$).

Conclusions Taken together, these results suggest that long-term rotating night shift work particularly early in career may be associated with an increased risk of breast cancer, which appears to diminish after nightshift work ceases. Future studies are needed

to confirm these findings and should explore the potential for tailored risk factor counselling in nightshift workers.

0363 MARGINAL STRUCTURAL MODELS TO ACCOUNT FOR TIME-VARYING CONFOUNDING VARIABLE AND THE HEALTH WORKER SURVIVOR EFFECT (FOR A MINI-SYMPOSIUM ON ‘DYNAMICS OF EXPOSURE AND DISEASE’, ORGANISED BY VERMEULEN)

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Objectives Marginal structural models (MSMs) in longitudinal studies are needed when time-varying confounders are themselves predicted by previous exposure, and are intermediate variables on the pathway between exposure and disease. The epidemiologist is left with the unenviable choice of adjusting or not for the confounder/intermediate variable. An example would be whether aspirin decreases cardiovascular mortality, in which the confounder/intermediate variable is cardiovascular morbidity.

Method MSMs use inverse-probability weights based on an ‘exposure’ model which assesses the probability that each subject has received their own exposure and confounder history up to time t , with the follow-up period divided into T ($t=1$ to T) categories. These weights are then used in standard regression models (eg., pooled logistic regression models across T categories) relating exposure to disease. Their use creates a pseudo-population where time-varying confounding is eliminated.

Results Empirical results show that standard methods to control for time-varying confounders can result in bias towards the null, compared to MSMs. A recent simulation study showed MSMs lead to unbiased results under a variety of assumptions.

Conclusions Some studies have used somewhat different but related methods (“g-estimation”) to account for the healthy worker survivor effect, where employment status is a time-varying confounder which predicts future exposure and may predict disease, but may also act as an intermediate variable because prior exposure may cause illness which results in leaving employment. Here we will present an overview of MSMs and the related g-estimation models.

0367 RATIONAL FOR CHOOSING EXPOSURE METRICS: A SHORT HISTORY

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Objectives Risk of chronic disease may be governed not only by cumulative levels of exposure but also by dynamic aspects of the exposure history. These dynamic aspects include characteristics of the exposure history itself (such as duration of exposure or time-varying intensities of exposure) as well as aspects of age-related susceptibility. This workshop will provide an overview of methods developed to better understand the dynamic aspects of exposure in epidemiological models.

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Results The presentations will provide examples of how such models can offer a richer description of epidemiologic associations. Insights may be important when risk assessments are based on epidemiologic results that assess cumulative exposures without consideration of exposure patterns or age-related susceptibility.

Conclusions Models that encompass dynamic aspects of exposure should be encouraged in risk modelling. Such models may also provide information about biologic pathways of disease, leading to better understanding of (for instance) the impact of metabolic saturation on the observed exposure–response curve, or the natural progression of the disease.

0368 DISENTANGLING THE EFFECT OF EXPOSURE DURATION, INTENSITY, AND TIME SINCE EXPOSURE IN STUDIES OF CHRONIC HEALTH EFFECTS

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Objectives Due to their interrelatedness, modelling independent effects of intensity, duration, and time since exposure on disease risk is complex. The indiscriminate use of the cumulative exposure metric (product of intensity and duration of exposure) might bias reported associations between exposure to hazardous agents and disease risk. We explored the use of a general framework to flexibly model the effects of intensity, duration, and time since exposure on chronic disease.

Method We will provide examples of models falling within the flexible framework. One of such models is an excess relative risk model that is linear in cumulative exposure and exponential in the intensity (or duration) of exposure and time since cessation. This model has been applied successfully to explore effect modification of cumulative exposure by intensity (or duration) of exposure for a number of exposures. We will demonstrate the application of this model in two studies of smoking and chronic disease.

Results In our example the excess relative risk model generally fits the data best. In both studies we observed a strong effect of time since cessation. We observed effect modification by intensity of smoking in one study.

Conclusions Application of flexible models will provide insight into whether the use of cumulative exposure in an epidemiological analysis is justified or whether reducing complex exposure history to a metric such as cumulative exposure is overly restrictive. Combining information on observed patterns of effect modification with mechanistic insights might contribute to the incorporation of biological hypotheses in the development of more biologically relevant exposure metrics.

0376 PROTRACTING EXPOSURES

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Objectives When an exposure is protracted or repeated over time, questions arise regarding variation in the effect for different temporal patterns of exposure. We review approaches to describe variation in an exposure's effect as a function of age-at-exposure, time-since-exposure, and exposure rate. These models implicitly assume that the effect of an exposure increment on subsequent disease risk depends upon its intensity and time-since-exposure, but not upon the intensities of prior exposures.

Then, we consider the possibility that the effect of an exposure is dependent upon earlier exposures. We use the term 'desensitisation' to refer to the scenario in which a person's response to an exposure diminishes if they have been previously exposed to it. We use the term 'sensitisation' to refer to the scenario in which a person becomes more susceptible to the effect of an exposure if they have been previously exposed to it.

Method We propose a general model for analysis of disease rates in a setting of protracted or repeated exposure that encompasses (de)sensitisation. We illustrate the model using empirical data from a cohort mortality study.

Results The presentation provide examples of how such models can offer a insights into a notion of interaction between an exposure at one point in time and later exposure to the same agent.

Conclusions The possibility that an exposure's effect may depend upon prior exposure to it is often considered in narrative descriptions of etiological processes, yet not readily accommodated by most standard approaches for analysis of protracted occupational and environmental data.

0377 REPRODUCTIVE EFFECTS OF WORKING NIGHT AND ROTATING SHIFTS

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Objectives Recent studies suggest that shift workers who experience exposure to light at night could be at increased risk for adverse reproductive outcomes.

Method Defined by cyclical patterns of circulating hormones, the reproductive system is vulnerable to shifts in circadian rhythms, either through sleep disturbances, altered melatonin production, exposure to light at night, or some other mechanism. Several occupational groups, including health care workers, law enforcement, firefighters, and manufacturing workers are required to work night shifts. Worldwide, millions work at least one night per month.

Results Research will be reviewed on shift work and reproductive outcomes, including menstrual cycle patterns, fertility, pregnancy loss, preterm delivery, and birth weight. The limitations of current research will also be discussed: is there a dose response effect from the number of years of shift work, or can the effects be reversed once shift work stops? Are there different effects from permanent night shift versus rotating shift involving nights?

Conclusions Future research needs will be identified, including the need for validation of self-reported shift work data and the mechanisms by which shift work affects reproductive health. Recommendations for shift workers and employers will be explored.

0380 DYNAMICS OF EXPOSURE AND DISEASE PROGRESSION: THE USE OF COMPARTMENTAL MODELS

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Objectives Chronic diseases are usually slow-developing condition and their risk may result from both long-term exposure and successive exposure increments, hence calling for models accounting for dynamics of exposure and disease progression.