

**Results** We found 8 and 897 CpG sites differentially methylated in former and current smokers, while compared to never smokers, respectively. The 8 candidate markers of former smoking showed a gradual reversion of their methylation levels from those typical of current smokers to those of never smokers. Further analyses using cumulative (over varying time windows) smoking intensities, highlighted three classes of biomarkers: short and long term biomarkers (measuring the effect of smoking in the past 10, and in the past 10 to 30 years respectively), and lifelong biomarkers detected more than 30 years after quitting smoking.

**Conclusions** Genome-wide DNA methylation profiles show promising abilities to detect short-term to lifelong biomarkers of tobacco smoke exposure and, more generally, to potentially identify time-varying biomarkers of exposure.

**0222 NIGHT WORK AND BREAST CANCER RISK AMONG WOMEN IN THE PUBLIC DANISH HEALTH CARE SECTOR - A SHORT-TERM FOLLOW UP OF A LARGE SCALE POPULATION**

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**Objectives** Experimental evidence suggest a short-term effect of light at night on breast cancer oncogenesis. We studied the short-term effect of night work on breast cancer occurrence.

**Method** We established a large, national cohort of employees in the public health care sector with a high prevalence of night shift work and with detailed data regarding occupational title and date and hour for beginning and end of every work duty: The Danish Working Hour Database (DWHD). DWHD encompasses payroll data as of 2007 and is updated on an annual basis. For this analysis we defined night work as at least 3 h of work between midnight and 05:00. From national cancer registers we retrieved information about breast cancer diagnosis for all female workers and their relatives. Reproductive history, hormone medications, attendance in mammography screening, and vital status were obtained from other national health registries.

**Results** The 6-year follow up from 2007 to 2012 included 169.011 women of which 98.297 (58%) had ever worked nights during the follow up. A total of 1.281 breast cancer cases occurred within the study population. 846 cases occurred among women never worked nights and 435 cases among women ever worked nights.

**Conclusions** Internal risk assessment of this dataset that includes alternative exposure metrics based on day-to-day night work exposure information will be presented.

**0223 MARGINAL STRUCTURAL MODELS IN OCCUPATIONAL EPIDEMIOLOGY: AN APPLICATION IN THE US ALUMINIUM INDUSTRY**

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**Objectives** To apply Marginal Structural Models (MSM) to address healthy workers survivor effect in a cohort study of active workers when time varying variables on health status and exposure are measured.

**Method** We used Cox MSMs and inverse probability weighting to assess the effect of PM<sub>2.5</sub> exposure on incident ischaemic heart disease (IHD) in an active cohort of 11 966 US aluminium workers. The outcome was assessed using medical claims data from 1998 to 2012. Quantitative exposure metrics of current exposure to PM<sub>2.5</sub> were dichotomized using different cutoffs and effects were assessed separately for smelters and fabrication. Risk score based on insurance claims was available as a time varying health status variable.

**Results** Defining binary PM<sub>2.5</sub> exposure by the 10th percentile cut-off, health status was affected by past exposure and predicted subsequent exposure in smelters, but not in fabrication. A Traditional cox model was appropriate for fabricators; the hazard ratio was 1.51(95% CI: 1.12 – 2.06) and was attenuated when considering higher exposure cutoffs. In smelters, Cox MSM Hazard Ratios for IHD comparing the effect of exposure in a population had everyone always been exposed to everyone always unexposed, using the 10<sup>th</sup> percentile exposure cutoff was 1.83 (95% CI: 1.14 – 2.94). Higher exposure cutoffs also resulted in attenuated effects.

**Conclusions** Marginal Structural Models can be used in active employment occupational cohorts to address time varying confounding. Results from the current study suggest that occupational exposure to PM<sub>2.5</sub> in the aluminium industry increases the risk of IHD in both smelters and fabrication.

**0224 DIRECT EXPOSURE TO METALWORKING FLUID AEROSOLS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN A COHORT OF U.S. AUTOMOTIVE INDUSTRY WORKERS**

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**Objectives** Exposure to metalworking fluid (MWF) causes respiratory outcomes such as asthma and chronic bronchitis, as well as symptoms including phlegm and wheezing. Chronic obstructive pulmonary disease (COPD) encompasses these outcomes, and so is a potential result of MWF exposure. Recent evidence based on g-estimation suggests that reducing exposure to MWF would substantially decrease years of life lost due to COPD. The objective of this analysis is to examine the exposure-response relationship between direct exposure to MWF and COPD mortality in a large occupational cohort.

**Method** Hazard ratios were estimated using Cox proportional hazards models for the association between cumulative exposure to the thoracic fraction (PM<sub>9,8</sub>) of straight, synthetic, or soluble MWF and COPD mortality. Subjects directly exposed to each fluid type were compared to those who were never directly exposed (assembly workers).

**Results** Hazard ratios for exposure quartiles increased in a non-monotonic fashion, with a maximum of 1.6 for straight, 1.4 for soluble, and 1.5 for synthetic, reflecting an increased risk of COPD for exposed subjects. However, none of the HRs were significant at the 95% confidence level. Indirect adjustment for