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CAUSAL MODELS FOR ADDRESSING HEALTHY WORKER EFFECT IN OCCUPATIONAL COHORT STUDIES. *J Chevrier, E A Eisen (University of California, Berkeley, CA 94720)

Individuals who are hired and remain at work longer are generally healthier than those who are unemployed or leave work, causing downward bias in studies of the health effects of occupational exposures. We present results from a study of ischemic heart disease mortality in a cohort of autoworkers exposed to metalworking fluid (MWF) using two approaches designed to reduce the bias. MWF is a mixed particulate containing metals and polyaromatic hydrocarbons and although previous studies of this cohort have found associations with selected cancers, this is the first investigation of heart disease. The cohort includes all workers hired between 1938 and 1981 who worked more than 3 years in one of three automobile manufacturing plants in Michigan (N = 39,927). The cohort was followed-up for vital status from 1941 to1995, and cause of death was ascertained from state health records and the National Death Index. Date of birth, race, gender and work history, including time off work, were obtained from company records. Annual exposure to oil-based MWF was treated as binary and health status was defined as the time off work in every year of follow up. To adjust for time off work as a time-varying confounder, we used two causal modeling approaches: Marginal Structural Models with Inverse Probability of Treatment Weights (IPTW) and Structural Nested Models using g-estimation. We compared these results based on 2,725 heart disease deaths, with those from a standard Cox model. Finally, we applied the same three approaches to examine MWF exposure in relation to all causes of death combined and all cancers combined in order to examine the hypothesis that bias due to healthy worker effect is stronger for chronic diseases, such as heart disease, than for cancer.

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STRUCTURAL MODELS FOR THE EFFECT OF OCCUPATIONAL ASBESTOS EXPOSURE ON LUNG-RELATED MORTALITY. *S R Cole, D B Richardson (Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC 27510)

Inferences from prior research regarding occupational exposure to asbestos fibers in textile plants and lung-related mortality may be susceptible to health worker survivor bias. We re-analyze a cohort of 3072 individuals occupationally-exposed to asbestos fibers in South Carolina and followed 61 years between 1940 and 2001 for lung-related mortality. Average asbestos concentrations, in units of chrysotile fiber-years/ml, were estimated using a previously-validated job exposure matrix. At work initiation, the 3072 had an average age of 26±8.3, was 59% male and 81% Caucasian. During 119142 person-years follow up, 184 lung-related and 1681 other deaths occurred. Of the 1207 participants who were not observed to die, 857 (71%) were still under follow up in 2001. 85 and 10% of person-years had a 0 dose and cumulative dose of asbestos exposure, respectively. The median (quartiles) cumulative dose was 3.92 (0.93, 15.85) fiber-years/ml of asbestos exposure. We fit standard Cox proportional hazards models with time varying asbestos exposure with and without adjustment for time varying work status. Also, we fit, by g-estimation, Robin's rank-preserving structural nested accelerated failure time model. For the latter, inferences are made under four central assumptions: consistency, no interference, no unmeasured confounding and no unmeasured informative drop out. Three necessary (but insufficient) conditions for the healthy worker survivor effect to bias the estimation of the association of cumulative asbestos exposure with lung-related mortality were observed and will be described. Results of standard and structural models will be presented.

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USE OF ANTIDEPRESSANTS DURING PREGNANCY AND THE RISK OF PRETERM DELIVERY AND FETAL GROWTH RESTRICTION. *S Toh, A Mitchell, C Louik, M Werler, C Chambers, S Hernández-Díaz (Harvard School of Public Health, Boston, MA 02115)

The associations between prenatal exposure to antidepressants and prematurity and fetal growth restriction are controversial and poorly understood. We studied the relation between antidepressants and these outcomes. This retrospective cohort study included women with non-malformed infants interviewed in the Slone Epidemiology Center Birth Defects Study between 1998 and 2008. We estimated odds ratios (OR) and 95% confidence intervals (CI) for prematurity and small for gestational age (SGA) offspring, adjusting for sociodemographic, lifestyle, and reproductive factors. The frequency of preterm delivery was 7.3% among the 5,710 non-users (reference), 8.9% among the 192 selective serotonin reuptake inhibitor (SSRI) users (OR 1.1; 95% CI: 0.6-2.0), and 15.3% among the 59 non-SSRI antidepressant users (OR 2.2; 1.0-4.9); the respective frequencies of SGA offspring were 7.2%, 10.9% (OR 1.7; 1.0-2.7) and 13.6% (OR 2.2; 1.0-4.9). Compared to non-users, the frequency of preterm delivery (7.6%) and SGA offspring (5.7%) were not increased among the 106 women who discontinued SSRIs before the end of the first trimester. However, among women who continued SSRIs beyond the first trimester, 10.5% delivered preterm (OR 1.3; 0.6-2.8) and 17.4% had SGA offspring (OR 3.0; 1.7-5.5). Women treated with SSRIs late in pregnancy had a higher frequency of SGA infants, and women receiving non-SSRI antidepressants were more likely to deliver premature and SGA offspring. Findings suggest an effect of underlying mood disorder or an effect common to both drug classes. In any case, prenatal antidepressant use may help identify women at elevated risks of delivering preterm and SGA infants.

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DYNAMIC MARGINAL STRUCTURAL MODELS TO FIND OPTIMAL TREATMENT REGIMES. *L E Cain, M A Hernán (Harvard School of Public Health, Boston, MA 02115)

The optimal time to initiate combined antiretroviral therapy to maximize a patient's AIDS-free survival is unknown. Randomized trials that compare regimes of the form ''initiate therapy when CD4 cell count first drops below x cells/μl,'' where x takes the values 200 to 500 by 10 cells/μl, would answer this question but are unlikely to be conducted. We mimicked these trials using observational data from the HIV-CAUSAL collaboration, one of the largest follow-up studies of HIV-infected patients. We excluded those patients who we did not observe the first time their CD4 cell count dropped below 500 cells/μl and those who initiated therapy before the first time their CD4 cell count dropped below 500 cells/μl. Each patient's baseline data may be consistent with her following several regimes. Therefore, we expanded the dataset by creating as many replicates of each patient as regimes the patient followed at baseline. We then used the time-varying CD4 count and treatment initiation data to identify if and when a replicate deviated from her baseline regime. We artificially censored the replicates at those times, and estimated inverse probability weights to adjust for the potential selection bias introduced by the artificial censoring. Finally, we compared the survival of the uncensored patients by fitting an inverse probability weighted Cox proportional hazards model that smoothes over the relative effects of the dynamic regimes and includes the baseline confounders as covariates. To our knowledge, this work represents the first large scale application of marginal structural models to compare the effects of dynamic regimes on survival.

 * = Presenter; S = The work was completed while the presenter was a student