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A SIMULATION STUDY OF RELATIVE EFFICIENCY AND BIAS IN THE NESTED CASE-CONTROL STUDY DESIGN. *Stephen Bertke, Misty Hein, Mary Schubauer-Berigan, James Deddens (Centers for Disease Control and Prevention, Cincinnati OH 45226)

Purpose: The nested case-control study design, in which a fixed number of controls are matched to each case, is often used to analyze exposure-response associations within a cohort. It has become common practice to sample 5 – 10 controls per case, however, previous research has shown that in certain instances, significant gains in relative efficiency can be realized when more controls are matched with each case. This study expanded upon these results through a simulation study by also considering a continuous exposure variable as well as investigating potential bias due to small sample sizes. Methods: A simulation study was conducted investigating the effect of the number of cases, strength of exposure-response relation and skewness of exposure variable on bias and relative efficiency. Results: It was shown that relative efficiency decreased and bias away from the null increased as the true exposure-response parameter increased and the skewness of the exposure distribution of the risk-sets increased. This became more pronounced when the number of cases in the cohort was small. Conclusions: Gains in relative efficiency and bias reduction can be realized by sampling more than the 5-10 controls per case generally recommended, especially when there are few cases, a strong exposure-response relation and a skewed exposure variable.

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BIAS ASSOCIATED WITH SYSTEMATIC ERROR IN A BINARY DEPENDENT REGRESSION VARIABLE. *Gary Fraser, Michael Orlich (Loma Linda University, Loma Linda CA 92350)

When disease endpoint data are ascertained by questionnaire for instance, it is likely that the positive and negative predictive values(PPV, NPV) will deviate from 1.0, often substantially. Moreover, it is possible that these errors may depend in part on the exposure of interest. We restrict attention to a binary exposure, for simplicity. For instance, the accuracy of self-report diagnoses will probably depend on interactions with the medical care system, may in turn depend on education, BMI, dietary patterns etc., factors which could also be the exposures of interest. Even if PPV and NPV do not depend on the exposure, where they are less than 1.0, in general this will still cause bias. An equation and examples describing this will be presented. Let D refer to true disease assignment, d to self-report; P is true prevalence, OR is odds ratio, $j = 0, 1$ refers to the two levels of the exposure variable, and RB_β(relative bias of logistic β) $= (\beta_d - \beta_D)/\beta_D$. An example illustrating the results of such errors is where $P_0 = 0.02$; $P_1 = 0.03$; so $OR_D = 1.515$; Let NPV = 0.99; PPV = 0.80, both equal for j = 0,1. Then $OR_d/OR_D = 1.337$, and $RB_\beta = 0.711$, a serious bias. Metrics (θ_j, δ_j) different from PPV and NPV, that describe false positive and false negative errors, result in a simple equation to describe bias, and also easily identify rare situations where such errors cancel each other. This equation is $OR_d/OR_D = (\delta_1.\theta_0)/(\delta_0.\theta_1)$, where θ and δ refer respectively to the relative distances that PPV (NPV) are through the range of their possible values. This assumes that PPV > P, and NPV > 1-P i.e. the self-report carries some information about D. Figures will illustrate the effects of such errors in dependent variables to cause bias. We conclude that, in the absence of a corrective procedure, perhaps based on a calibration sub-study, regression analyses where there are more than trivial proportions of false positives or negatives, will often be seriously biased.

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RESPONSE RATE AND TIME TO RESPONSE FOR PATIENT REPORTED OUTCOMES COLLECTED USING A CENTRALIZED SYSTEM IN TWO AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK CANCER SCREENING TRIALS. *Ilana Gareen, Fenghei Duan, Brad Snyder, JoRean Sicks (Brown University, Providence RI 02912)

Patient Reported Outcomes (PRO) are increasingly recognized as clinically important endpoints. We used a central Outcomes and Economics Assessment Unit (OEAU) to administer questionnaires at time points that did not correspond with a clinic visit for two American College of Radiology Imaging Network (ACRIN) screening trials: the National Lung Screening Trial (NLST) and the National CT Colonography Trial (NCTCT). The NLST questionnaire was mailed at 1 month post-screen and included standardized quality of life tools. The NCTCT questionnaire was mailed at 2 weeks post-screen and collected data on procedure preference and intent to return for future screens. In both studies, questionnaire return was requested within 30 days of mailing. Questionnaires were accepted until 180 days of mailing. OEAU staff monitored participant responses and encouraged form completion. We assessed factors associated with questionnaire return using a log multinomial model (return < 30 days, 30-180 days, or not returned). 90% of the NLST questionnaires and 87% of NCTCT questionnaires were returned to the OEAU within 180 days. In NLST, late response was positively associated with increasing age for black women: Risk Ratio[RR] (5 year increase) = 1.79 (95% confidence interval [CI]: 1.36,2.36), but was inversely associated with late response for white men: RR (5 year increase) = 0.73 (95% CI:0.65,0.83). In the NCTCT, which recruited a younger population, late response was inversely associated with younger age, RR(5 year increase) = 0.90 [95% CI: 0.83, 0.98]. We demonstrated that PROs can be effectively collected from a central site in multi-center trials and identified factors associated with late and non-response. In future studies, we can focus additional efforts on populations less likely to return questionnaires in a timely fashion. This study was supported by the National Cancer Institute through the grants U01 CA079778 and U01 CA080098.

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INFLUENCE OF CYP2A6 *4 GENOTYPES ON SERUM COTININE AMONG NON-SMOKING CHINESE PREGNANT WOMEN: IMPLICATION FOR SECONDHAND SMOKE MEASUREMENT. *Chuanbo Xie, Xiaozhong Wen, Peng Ding, Tao Liu, Yanhui He, Zhongzheng Niu, Xiaoying Wu, Shanyu Zhou, Jianmiao Lin, Xiaoling Guo, Weiqing Chen (Department of Biostatistics and Epidemiology, School of Public Health, Sun Yat-Sen University, Guangzhou Guangdong China)

Objective: To investigate the influence of CYP2A6*4 genotypes on serum cotinine among non-smoking pregnant women and assessed its implication for measuring secondhand smoke (SHS) exposure during pregnancy. Methods: We analyzed 545 Chinese non-smoking pregnant women enrolled in a case-control study on SHS and birth outcomes in Guangdong, Southern China. Participants self-reported their SHS exposure status and duration during pregnancy in hospital for delivery. PCR was used for CYP2A6*4 genotyping, and ELISA for measuring serum cotinine. We stratified women by their self-reported SHS exposure status and CYP2A6*4 genotypes, and then compared their median concentration of serum cotinine among women with Kruskal-Wallis and Nemenyi tests. Results: In our sample, 16.3% of pregnant women had CYP2A6*4 allele; and the genotype frequencies of CYP2A6*1/*1, CYP2A6*1/*4 and CYP2A6*4/*4 were 69.7%, 27.9% and 2.4%, respectively. Pregnant women who self-reported SHS exposure have higher median serum cotinine (3.06 ng/ml) than those who self-reported non-SHS exposure (2.27 ng/ml). Among women who self-reported non-SHS exposure, the median cotinine levels were 2.83, 1.39 and 0.77 ng/ml for those with CYP2A6*1/*1, CYP2A6*1/*4 and CYP2A6*4/*4 genotype, respectively. Among women who self-reported SHS exposure, the median cotinine levels were 3.32, 2.37 and 1.56 ng/ml for those with CYP2A6*1/*1, CYP2A6*1/*4 and CYP2A6*4/*4 genotype, respectively. Strikingly, self-reported SHS exposed women with CYP2A6*1/*4 or CYP2A6*4/*4 genotype had significantly lower (rather than higher) median cotinine level than self-reported non-SHS exposed women with CYP2A6*1/*1 (P-value, 0.012). Conclusion: In our sample, CYP2A6*4 genotype was associated with lower serum cotinine among non-smoking pregnant women. Measuring CYP2A6*4 genotype may help to improve the validity of SHS measure by serum cotinine among pregnancy women.