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Assessing Exposure-Response Trends Using the Disease Risk Score

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To the Editor:

Standardization by a disease risk score (DRS) may be preferable to weighting on the exposure propensity score if the exposure is difficult to model (1), relatively novel (i.e., newly emerging or rapidly-evolving), or extremely rare (2, 3). For exposures with more than two levels, methods are lacking for a DRS-based approach. We present an approach to estimate trends in standardized risk ratios (RRs) based on a regression model that uses a DRS.

Let *Y* denote a binary outcome, *X* denote a fixed exposure of interest that is classified into *P*+1 groups 0, 1, ..., *P*, where *X*=0 is the referent, and ***Z*** denote potential confounders of associations between *X* and *Y*. Suppose that the investigator wants to estimate RRs standardized to the covariate distribution in each exposed group,

$$RR(p)=\sum_{Z}\frac{\Pr(Y|X=p)}{\Pr(Y|\boldsymbol{Z}=\boldsymbol{z},X=0)}Pr(\boldsymbol{Z}=\boldsymbol{z}|X=p).$$

Let $\Pr(Y=1|\boldsymbol{Z}=\boldsymbol{z},X=0)=F(\boldsymbol{Z}=\boldsymbol{z},X=0)$ denote the DRS, which we estimate by fitting a logistic regression model to the empirical data for the referent group and set $\hat{F}(Z=z_i,X=0)$ equal to the predicted probability of the outcome for each cohort member.

Following Breslow and Day (1987) who demonstrated that a standardized ratio measure could be estimated by using an external standard as an offset in a multiplicative regression model (4) (page 151), estimates of *RR*(*p*) can be obtained using just the records for exposure groups *p*>0, fitting a model of the following form to the data,

$$\frac{\Pr(Y|\boldsymbol{Z}=z,X=p)}{\hat{F}(\boldsymbol{Z}=z,X=0)}=\exp\left(\beta_1+\sum_{p=2}^{P}\beta_p(I[X=p])\right)$$

$$=\log(\Pr(Y|\boldsymbol{Z}=\mathrm{z},X=p))=\beta_1+\textstyle\sum_{p=2}^{P}\beta_p(I[X=p])+\log(\hat{F}(\boldsymbol{Z}=z,X=0))\text{….Equation 1,}$$

where *I*[‘logical expression’] is an indicator function that returns a value of 1 if ‘logical expression’ is true, else 0, and $\log(\hat{F}(\boldsymbol{Z}=z,X=0))$ is a model offset.

Given this parameterization, $\hat{\beta}_p$ describes the change in the standardized log-RR estimate for each exposure level ($p \geq 2$) relative to the log-RR estimate for the first exposure category (X=1). Each log-RR may be standardized to a different target population; therefore, a comparison of standardized RRs between exposure group p and another group r ($\neq p$) may be complicated by the fact that the groups are not mutually standardized. Nonetheless, we illustrate two settings in which our approach can be used to assess an exposure–response trend.

1) When covariates $\boldsymbol{Z}$ are similarly distributed across the non-referent levels of X

One setting arises when the distribution of covariates $\boldsymbol{Z}$ is similar for exposure groups X=1 and exposure groups p>1; note that the referent (X=0) may differ with respect to $\boldsymbol{Z}$ from non-referent groups (X>0). This condition is readily assessed by examination of the distributions of $\boldsymbol{Z}$ across non-referent levels of X. While this condition may seem trivial, it may hold in a variety of epidemiological research areas (eAppendix 1; http://links.lww.com/EDE/B621).

2) When risk ratios are homogeneous across strata of covariates

Another setting arises when there is homogeneity of the RRs across strata defined by the cross-classification of discrete levels of covariates, $\boldsymbol{Z}$ (we assume that strata may be defined for purposes of assessments of homogeneity). We propose a random effects model to assess this condition (eAppendix 2; http://links.lww.com/EDE/B621) and undertook simulations to illustrate the approach and as confirmatory of the mathematical theory considered (eAppendix 3; http://links.lww.com/EDE/B621).

We propose a modeling approach that uses the DRS to obtain standardized RRs where the target population for standardization is the exposed members of the study population in each exposure group. When stratum-specific RRs are approximately homogenous, a trend assessed as the difference in log-RRs will tend to conform closely to the trend that would be obtained for an analysis of RRs that have been mutually standardized to a common target population. The approach is potentially useful for estimation of risk or prevalence ratios for contrasts defined by a point exposure with more than two levels in a study.

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