Negative Control Outcomes and the Analysis of Standardized Mortality Ratios

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Abstract: In occupational cohort mortality studies, epidemiologists often compare the observed number of deaths in the cohort to the expected number obtained by multiplying person-time accrued in the study cohort by the mortality rate in an external reference population. Interpretation of the result may be difficult due to noncomparability of the occupational cohort and reference population with respect to unmeasured risk factors for the outcome of interest. We describe an approach to estimate an adjusted standardized mortality ratio (aSMR) to control for such bias. The approach draws on methods developed for the use of negative control outcomes. Conditions necessary for unbiased estimation are described, as well as looser conditions necessary for bias reduction. The approach is illustrated using data on bladder cancer mortality among male Oak Ridge National Laboratory workers. The SMR for bladder cancer was elevated among hourly-paid males (SMR = 1.9; 95% confidence interval [CI] = 1.3, 2.7) but not among monthly-paid males (SMR = 1.0; 95% CI = 0.67, 1.3). After indirect adjustment using the proposed approach, the mortality ratios were similar in magnitude among hourly- and monthly-paid men (aSMR = 2.2; 95% CI = 1.5, 3.2; and, aSMR = 2.0; 95% CI = 1.4, 2.8, respectively). The proposed adjusted SMR offers a complement to typical SMR analyses.

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Evaluations of potential carcinogens, such as those conducted by the International Agency for Research on Cancer and the National Toxicology Program, play an important role in occupational and environmental protection.[1,2] For an agent to be classified as a known carcinogen, typically there must be evidence from studies of human populations; often, such epidemiologic evidence derives from occupational cohort mortality studies.

One of the commonly used measures of relative mortality in occupational cohort studies is the ratio of observed to expected deaths, the latter obtained by multiplying person-time accrued in an occupational cohort by the mortality rate in an external reference population, usually all residents of a nation or region. When the expected number is computed by taking into account some covariates by standardization, the observed-to-expected ratio is called a standardized mortality ratio (SMR).

Assuming that the reference population mortality rates accurately represent the mortality rates that would have been observed if the occupational cohort was not exposed to the potential carcinogen of interest, the SMR quantifies the effect of the potential carcinogen on mortality rates. If the assumption does not hold then the SMR may yield a biased estimate of this effect measure due to confounding. This potential for bias poses an important obstacle to the use of SMR analyses in the evaluation of an agent's role as a human carcinogen. An SMR of unity could reflect absence of an exposure effect, or it could reflect bias that is masking the exposure's effect. Judgments regarding the direction and magnitude of bias in SMRs therefore play a role in interpreting this type of evidence when used for such evaluations. The ubiquity of SMRs below unity for major categories of cause of death in occupational cohort studies, often referred to as "the healthy worker effect" has led some authors to advocate for abandoning SMR analyses altogether.[3]

We describe an approach to estimate an adjusted standardized mortality ratio (aSMR) to reduce bias in SMR analyses. The approach draws on methods developed for the use of negative control outcomes.[4] The purpose of the negative control is to reproduce conditions that cannot involve the causal effect of exposure but do involve the same sources of bias that affect the association of primary interest. Conditions necessary for unbiased estimation are described, as well as looser conditions necessary for reduction of bias in the adjusted estimate relative to the standard SMR.

METHODS

The setting of interest is an evaluation in which occupational cohort mortality data are used to assess whether an

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agent is a human carcinogen. Suppose we stratify the study cohort into $k = 1 \ldots K$ subgroups based on levels of confounders (e.g., 5-year categories of age), where I_{1k} is the observed rate of death due to the outcome of interest in the cohort in stratum k, and I_{0k} is the counterfactual rate of death due to the outcome of interest that would have been observed had the cohort not been exposed to the occupational carcinogen of interest.

Within each stratum k, we wish to compare the rate of death due to the outcome of interest to the rate that would have been observed if the occupational cohort had not been exposed to the carcinogen of interest. A simple comparative statistic, for each stratum, is the rate ratio:

$$\frac{I_{1k}}{I_{0k}} = \exp(\alpha_k), \text{ for } k = 1 \ldots K, \quad (1)$$

with α_k denoting the log of the stratum-specific rate ratios, as when estimated in a log-linear regression. The parameters, α_k, are the target parameters of primary interest that we would like to estimate.

However, we do not get to see the counterfactual rates, I_{0k}. Instead epidemiologists often calculate comparative statistics using stratum-specific external reference rates, I_{Rk}, that may differ from the counterfactual rates. We can denote this deviation by δ_k, using the expression

$$I_{Rk} = I_{0K}\exp(\delta_k), \text{ for } k = 1 \ldots K.$$

Comparing the observed stratum-specific rates in the cohort to the reference population rates yields

$$\frac{I_{1k}}{I_{Rk}} = \frac{I_{1k}}{I_{0k}\exp(\delta_k)} = \exp(\alpha_k - \delta_k), \text{ for } k = 1 \ldots K . \quad (2)$$

We might combine these stratum-specific rate ratios into a single summary figure; a weighted mean of the stratum-specific rate ratios can be obtained, where the weights are chosen to minimize the standard error of the weighted mean (Appendix). Usually an SMR is calculated for such data; if this is done using the usual formula then a numerically equivalent summary measure is obtained.[5] This is because the approach in the Appendix for calculating a weighted mean of the stratum-specific rate ratios is simply an alternative to the usual formula for calculating an SMR.[6,7]

If the reference population mortality rates accurately represent the mortality rates that would have been observed had the occupational cohort been unexposed (i.e., $\delta_k = 0$) then a summary SMR based on the external reference rates summarizes the stratum-specific causal rate ratio (Equation 1).[8] However, the ubiquity of SMRs below unity for major categories of cause of death in occupational cohort studies, often referred to as "the healthy worker effect," suggests a common problem of noncomparability of external reference rates to counterfactual rates.

Negative Control Outcome

We can adjust the rate ratios described by the expression in Equation 2 to better estimate the contrasts of interest (Equation 1) by leveraging assumptions external to the study data about a negative control outcome. The purpose of the negative control is to reproduce a condition that arguably cannot involve the causal effect of exposure but does involve the same sources of bias (confounding or selection) that affect the association of primary interest.[4,9,10] The Figure illustrates an ideal negative control outcome for our purposes. Occupational exposure is not a cause of the negative control outcome. There is an unmeasured factor, however, that is associated with occupational exposure, risk of death due to the outcome of interest, and risk of death due to the negative control outcome.

Suppose J_{1k} are rates of the negative control outcome in the occupational cohort, and J_{0k} are expected, possibly unobserved rates of the negative control in the absence of exposure. Again, stratum-specific external reference rates for the negative control, J_{Rk}, may differ from the expected, possibly unobserved rates for the negative control outcome in the absence of exposure; this difference can be described by the parameters, ε_k, under the model: $J_{Rk} = J_{0k}\exp(\varepsilon_k)$. An expression for the comparative statistic for the rate of the negative control outcome in the occupational cohort to the stratum-specific external reference rate for the negative control is

$$\frac{J_{1k}}{J_{Rk}} = \frac{J_{1k}}{J_{0k}\exp(\varepsilon_k)} = \exp(-\varepsilon_k), \text{ for } k = 1 \ldots K \quad (3)$$

because the rate of the negative control outcome is not affected by the exposure of interest. That is, we are assuming that our choice of negative control outcome satisfies $\frac{J_{1k}}{J_{0k}} = 1$.

Indirect Adjustment

Complete adjustment for confounding is possible if there is equivalence of bias magnitude for the negative control outcome (ε_k) and outcome of primary interest (δ_k). Using the negative control outcome, we can derive an adjusted comparative statistic for each stratum:

$$\frac{I_{1k}/I_{Rk}}{J_{1k}/J_{Rk}} = \exp(\alpha_k + \varepsilon_k - \delta_k), \text{ for } k = 1 \ldots K. \quad (4)$$

By calculating the weighted mean of the stratum-specific comparative statistics, where the weights are chosen

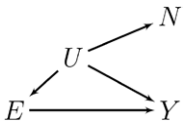

FIGURE. Directed acyclic graph illustrating an ideal negative control outcome. For one stratum, *k*. *E* denotes exposure, *Y* denotes outcome of interest, *N* denotes negative control outcome, and *U* denotes unmeasured causes of *E*, *N*, and *Y*.

to minimize the standard error of the weighted mean, a summary figure can be obtained. We refer to this summary figure as an aSMR.

Bias is reduced, although not entirely eliminated, as long as $|\varepsilon_k - \delta_k| < |\delta_k|$. This condition holds, for example, when $0 < \delta_k$, as long as ε_k falls within the range $0 < \varepsilon_k < 2\delta_k$, in every stratum, k. Therefore, over a wide range of conditions, the aSMR (derived from Equation 4) will yield a less biased estimate of the quantity of interest (Equation 1) than the traditional SMR (derived from Equation 2).

The Appendix provides SAS code for estimation of the aSMR and associated confidence intervals (CIs) and can be applied to data derived from a life table program that is freely available.[11,12] Table 1 lists the assumptions discussed above that are necessary for the aSMR to reduce bias.

Example: Methods

A cohort was assembled of male Oak Ridge National Laboratory (ORNL) workers who were hired before 1985 and who worked at least 30 days, with complete information on name, social security number, date of birth, and date of first hire. Vital status through December 31, 2008, was ascertained through searches of Social Security Administration records and the National Death Index (NDI). We used the NDI-Plus service to obtain underlying cause of death for deceased workers identified by the NDI. For deaths before 1979, cause of death information was coded according to the Eighth revision of the International Classification of Diseases; for deaths occurring in 1979 and later, cause of death information was coded to the International Classification of Diseases revision in effect at the time of death. If there was no death indication for a worker and they were confirmed to be alive on January 1, 1979 or later by the Social Security Administration or by ORNL's employment records then they were assumed to be alive as of December 31, 2008. Those lost to follow-up before January 1, 1979, were only considered alive until the date last observed. The mortality experience of the cohort was analyzed using the life table analysis system.[11,13] SMRs and aSMRs were compared, the latter estimated by modeling the observed number of deaths in strata defined by 5-year categories of age and calendar period, sex, and race (white or nonwhite). These analyses focus on deaths due to bladder cancer, where the occupational exposure of interest is ionizing radiation, and ischemic heart disease is taken as the negative control outcome for all calculation of aSMRs. We also report results of a sensitivity analysis conducted using diabetes as a negative control outcome. Analyses were conducted for subgroups defined by white-collar (monthly-paid) and blue-collar (hourly-paid) men. The study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill.

Example: Results

The study included 3,624 hourly-paid men and 7,335 monthly-paid men; the two groups had similar distributions of year of birth, year of hire, age at study entry, and length of follow-up (Table 2). The SMR for bladder cancer was elevated among hourly-paid males (SMR = 1.9; 95% CI = 1.3, 2.7, based on 29 deaths) but not among monthly-paid males (SMR = 1.0; 95% CI = 0.67, 1.3, based on 36 deaths). After indirect adjustment (Table 3), the mortality ratios were similar in magnitude among hourly- and monthly-paid workers (aSMR = 2.2; 95% CI = 1.5, 3.2; and aSMR = 2.0; 95% CI = 1.4, 2.8, respectively). The heterogeneity in SMR appears to be due to paycode differences in comparability of occupational cohort to reference rates, and this heterogeneity is reduced by the proposed indirect adjustment approach. In sensitivity analyses, we calculated mortality ratios among hourly- and monthly-paid workers when diabetes was taken as the negative control outcome (aSMR = 2.25; 95% CI = 1.56, 3.24; and aSMR = 2.61; 95% CI = 1.88, 3.62, respectively).

DISCUSSION

The illustrative analysis of mortality among ORNL workers shows how reducing bias arising from "healthy worker" effects reduced evidence of apparent heterogeneity in bladder cancer SMRs between hourly- and monthly-paid ORNL workers. A naive interpretation of the bladder cancer SMRs for hourly-paid (SMR = 1.9; 95% CI = 1.3, 2.7) and monthly-paid (SMR = 1.0; 95% CI = 0.67, 1.3) men might lead an investigator to conclude that this pattern reflects higher occupational exposure to bladder carcinogens among blue-collar than white-collar workers at this facility. However, prior research on radiation exposures at ORNL did not suggest that white-collar workers had substantially less exposure than blue-collar workers.[14] An alternative explanation is that the external reference rates are a better proxy for the counterfactual bladder cancer rates that would be observed for blue-collar workers than they are for the white-collar workers. The latter explanation is reasonable because white-collar workers at ORNL tended to be highly educated technical professionals who exhibited substantial deficits in mortality for a range of other smoking-related causes of death. The latter explanation is also

TABLE 1. Assumptions Required for the aSMR to Reduce Bias

i	The exposure of interest does not affect the rate of the negative control outcome
ii	There is an open backdoor path between the exposure of interest and outcome of primary interest, as well as with the negative control outcome (Figure)
iii	The direction of bias for the negative control outcome and outcome of primary interest is the same (i.e., ε_k and δ_k have the same sign), and $\lvert\varepsilon_k\rvert$ lies between zero and twice $\lvert\delta_k\rvert$

TABLE 2. Description of Cohort Characteristics

	Blue Collar (Hourly-paid)		White Collar (Monthly-paid)	
	N (%)		n (%)	
Vital status				
Alive	1,660	46	4,304	59
Dead	1,955	54	2,803	38
Lost to follow-up	9	0.20	228	3
Total	3,624	100	7,335	100
	Mean (Std Dev)		Mean (Std Dev)	
Year of birth	1929 (15)		1930 (14)	
Year of hire	1961 (11)		1962 (12)	
Age at entry (years)	32 (9)		31 (8)	
Length of follow-up (years)	37 (12)		39 (14)	

Men employed at Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1943–2008.

consistent with prior studies that have noted that the healthy worker bias may be greater for white-collar professional workers than for blue-collar workers.[15]

In an analysis of aSMRs, there was little evidence of heterogeneity in bladder cancer observed-to-expected mortality ratios between hourly- and monthly-paid workers. The findings of our illustrative analysis support the conclusion that the difference in bladder cancer SMRs by pay code among male Oak Ridge workers was an artifact of bias due to noncomparability of the counterfactual reference rates for white-collar workers and the external reference population. Such conclusions hold if one accepts that the conditions for the aSMR to yield less biased results appear reasonable in this example (Table 1).

Comparisons of SMRs between groups can produce misleading results if the person-time distribution differs between the groups and the stratum-specific mortality ratios are not equal. In such cases, SMRs may differ between groups even when stratum-specific mortality ratios do not differ. Richardson et al.[16] proposed an approach to reduce potential bias occurring in comparisons of SMRs in such cases. However, in our example, hourly- and monthly-paid men had similar years of birth, ages at entry into follow-up, and durations of follow-up, leading to similar person-time distributions in these two groups (Table 2).

TABLE 3. Traditional and Adjusted Standardized Mortality Ratios for Bladder Cancer

	Blue Collar (Hourly-paid)	White Collar (Monthly-paid)
Traditional SMR (95% CI)	1.9 (1.3, 2.7)	1.0 (0.67, 1.3)
Adjusted SMR[a] (95% CI)	2.2 (1.5, 3.2)	2.0 (1.4, 2.8)

Men employed at Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1943–2008.

[a]Indirect adjustment using ischemic heart disease as negative control.

Interpretation of the traditional SMR is challenging because the occupational cohort and reference population may differ (within strata of confounders, such as age and calendar period) with respect to factors other than the exposure of interest. This is a failure of the conditional exchangeability assumption.[17] The proposed aSMR offers a potentially useful complement to the classical SMR that may reduce confounding bias through indirect adjustment using a negative control outcome.

Under the ideal case of bias equivalence, there is complete elimination of bias in the adjusted SMR. However, failing the ideal case, under a wide range of conditions the adjusted SMR will be less biased than the standard SMR. Bias reduction occurs if ε_k and δ_k have the same sign, and $|\varepsilon_k|$ lies between zero and twice $|\delta_k|$. While the sign and magnitude of ε_k can be determined from the negative control outcome, δ_k is unknown. However, in settings where a healthy worker hire bias is expected, for example, δ_k might be considered positive. While these conditions are not testable assumptions, they would be supported if there is belief that a moderate or strong healthy worker bias was operating, and ε_k was relatively small.

Under certain conditions, we can relax the assumption of bias equivalence, yet still obtain complete control for confounding with this approach. If the relation between an unmeasured confounder (U) and the negative control outcome, and that between U and the potential outcome for the disease of interest in the absence of exposure (Y_0) are monotone at the individual level, then bias is eliminated entirely, even if the association between U and N is quite distinct from that between U and Y.[18]

Our illustrative example is not intended to reflect the ideal case of bias equivalence, but rather a setting in which the adjusted SMR may be less biased than the standard SMR. Prior studies have suggested minimal healthy worker bias for mortality due to cancer and noncancer causes among blue-collar workers.[15] In our example, we observed minimal impact of adjustment on the bladder cancer mortality ratio (i.e., the SMR was similar in value to the aSMR). Among white-collar professionals, prior studies suggested larger magnitudes of healthy worker bias for mortality due to cancer and noncancer causes, particularly for smoking-related causes of death.[15] In our example, we observed a substantial impact of adjustment on the bladder cancer mortality ratio, and believe this reflects bias reduction. In sensitivity analyses, we examined results using diabetes as a negative control outcome and observed similar findings.

Interestingly, Equation 4 can be equivalently expressed without reference to the observed person-time in the occupational cohort. This suggests an appealing aspect of the aSMR. Unlike the traditional SMR, the aSMR can be estimated in settings in which enumeration of person-time at risk is infeasible. For example, some occupational mortality studies draw upon a registry of events (deaths or disease) but do not have access to information necessary to calculate person-time

at risk.[19] The aSMR may be calculated as an alternative to the proportionate mortality ratio, which is often used in such settings.

Furthermore, we note that Equation 4 is algebraically equivalent to a stratum-specific mortality odds ratio.[20] Previous papers on mortality odds ratios framed the effect measure in terms of a cumulative case–control study design: cases represented events ascertained over a follow-up period and controls are selected from a set of reference causes of death.[21,22] In contrast, Equation 4 is expressed in terms of estimation of an underlying rate ratio parameter for a specified exposure contrast, using a negative control outcome to reduce bias in the stratum-specific rate ratio. This study provides a connection between earlier work on analysis of cohort data using a mortality odds ratio and contemporary work on the logic of analysis using negative control outcomes. In the previous literature on the mortality odds ratio, the choice of auxiliary cause of death was framed as the problem of identifying a set of causes of death for which exposure is not a risk factor (for mortality proportions). Extending this, we show that beyond using the negative control outcome as a reference outcome, it can be used for bias reduction. This becomes the basis for an approach to reduce a major limitation of SMR analysis: the "healthy hire bias."[23] Of course, a plausible negative control outcome that meets the assumptions may not be available in many settings.

We have framed the causal contrast of interest in terms of a ratio of the observed rate of an outcome of interest to the counterfactual rate of that outcome in the absence of exposure. The SMR is often discussed as the ratio of observed to expected deaths (rather than rates). These are equivalent assuming that exposure does not affect the distribution of person-time. The adjustment is premised on similar magnitudes of bias for the negative control outcome and outcome of interest within strata, k. Consequently, variation in the healthy worker bias is handled by the proposed adjustment as long as the net bias is comparable for the negative control outcome and the outcome of interest, even if bias from specific sources varies in magnitude.

Several recent papers have discussed use of negative controls for analyses of epidemiologic data.[4,9,10,24] This study, which focuses on analysis of mortality ratios, addresses use of negative control outcomes for bias reduction in such analyses. In this way, it extends prior work regarding confounding by smoking in occupational cohort analyses of exposure-lung cancer mortality associations.[10,24] The approach described in this article has connections to earlier work on qualitative interpretation of SMRs,[25] proportionate mortality ratios (PMRs),[15] and mortality odds ratios (MORs). This article is intended to further clarify the logic underlying adjustment of mortality ratios using a negative control outcome, and the conditions under which such an approach may reduce bias.

Interpretation of the traditional SMR requires one set of unverifiable assumptions (the reference rates represent the rate that would be seen in the cohort in the absence of exposure). Interpretation of the proposed aSMR requires a different set of unverifiable assumptions: the negative control outcome is not caused by the occupational exposure, but is impacted by similar bias factors (Table 1). Standard frequentist CIs do not capture uncertainty in such assumptions. While each approach requires unverifiable assumptions, the proposed aSMR may serve as a useful complement to traditional SMRs; in some cases, the opportunity to assess results under different assumptions regarding confounding may help investigators to better triangulate estimation of the true causal effects of interest.

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APPENDIX

We provide a simple tabular example to illustrate the data structure and SAS code that may be used to implement this approach.

The data in eTable 1 (http://links.lww.com/EDE/A952) were generated under a model where the true stratum-specific rate ratios for the outcome of interest equal two (i.e., $I_{1k}/I_{0k} = 2$) and the stratum-specific rate ratios for the negative control outcome equal unity (i.e., $J_{1k}/J_{0k} = 1$). Stratum-specific external reference rates differ from counterfactual rates, $I_{Rk} = I_{0k} \exp(\delta_k)$ and $J_{Rk} = J_{0k} \exp(\varepsilon_k)$, where $\delta_k = \varepsilon_k \neq 0$. The data in eTable 1 (http://links.lww.com/EDE/A952) consist of person-time and events for the outcome of interest, a negative control outcome, and external reference rates for the outcome of interest and the negative control outcome.

The four stratum-specific rate ratios are close in value and therefore it seems reasonable to combine them into a summary value. The standardized mortality ratio (SMR) can be calculated, in the usual manner, as $\Sigma Y_{1k}/\Sigma T_{1k} I_{Rk}$. This is equivalent to the weighted average of the stratum-specific rate ratios, $[Y_{1k}/T_{1k}]/I_{Rk}$, where the weight for stratum k is $T_{1k} I_{Rk}/\Sigma T_{1k} I_{Rk}$.

The data in eTable 1 (http://links.lww.com/EDE/A952) could be assembled in a SAS dataset and analyzed using the sample code provided in eFigure 1 (http://links.lww.com/EDE/A952). Using SAS PROC GENMOD, a Poisson regression model may be fitted to these data to estimate the SMR,[6] where the log of the product of the external reference rates and person-time serve as an offset (eFigure 2; http://links.lww.com/EDE/A952).

Adjusted SMR

The SMR 1.32 is a biased estimate of the desired summary rate ratio ($I_{1k}/I_{0k} = 2.0$) because $\delta_k \neq 0$. The manuscript proposes calculation of an adjusted SMR (aSMR) using a negative control outcome to reduce this form of bias. The aSMR can be obtained by fitting a Poisson regression model where the log of the product of the number of negative control outcome events and the ratio of external reference rates for the outcome of interest and negative control outcome serve as an offset (eFigure 3; http://links.lww.com/EDE/A952). We recommend the Poisson regression approach to facilitate obtaining adjusted SMRs and their associated confidence intervals. Note that in contrast to the traditional SMR (where the log of the product of the external reference rates and person-time serve as an offset), the aSMR can be calculated without information regarding the person-time at risk accrued in the study cohort (because the log of the product of the number of negative control outcome events and the ratio of external reference rates for the outcome of interest and negative control outcome serve as an offset).

The aSMR (aSMR = 2.00; 95% confidence interval = 1.72, 2.32) equals the desired summary ratio of the observed to counterfactual rates ($I_{1k}/I_{0k} = 2.0$; 95% confidence interval = 1.72, 2.32) because the reference rates for the negative control outcome, J_R, differ from counterfactual reference rates J_0 by a factor ε_k that equals δ_k.