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LETTER TO THE EDITOR

Re: Bias in the proportionate mortality ratio analysis of small study populations: A case on analyses of radiation and mesothelioma

Sir,

Studies of mortality in occupational groups frequently use proportionate mortality ratio (PMR) analyses (Steenland et al.1990). In the simplest case, the PMR is the ratio of the proportion of deaths due to a specific cause in the study population to the proportion of deaths due to the same cause in a referent population. Software packages such as the NIOSH Life-Table Analysis System (LTAS.NET) can estimate PMRs that are adjusted for gender, race, age, and calendar year (Schubauer-Berigan et al. 2011). Zhou (2014) recently claimed that the PMR reported in the NIOSH LTAS.NET program is biased under certain conditions - namely, when the number of deaths available for analysis is small relative to the number of cause-of-death categories, resulting in categories with zero observed deaths. To remove the bias, Zhou proposed an adjustment that involved excluding deaths from the referent population for categories with zero deaths in the sample when estimating the PMR. The objective of this letter is to point out faulty logic in Zhou's proposed adjustment and assure users of LTAS.NET that the PMR estimates produced by LTAS.NET are not biased.

First, when presenting the formula for estimating the PMR, Zhou makes a distinction between the number of cause-of-death categories with non-zero deaths in the study population (k) and the number with non-zero deaths in the referent population (m) and claims that the formula for the PMR is valid only when $k = m$. In fact, the PMR would be zero for causes of death observed in the referent population with zero deaths in the study population. Consider the example in Table I, which has five cause-of-death categories for the referent population ($m = 5$) but only three of these have deaths in the study population ($k = 3$). The usual PMRs are greater than 1 for categories 1–3 (reflecting the elevated proportion of deaths in these categories relative to the referent population) and 0 for categories 4 and 5. Zhou's 'adjusted PMRs' are quite different from the usual PMRs and in fact indicate a deficit of mortality for category 3. Zhou attributes this difference to a ''bias'' in the usual PMR formula when $k < m$. However, another way to handle categories with zero deaths in the study population would be to combine categories. Table II illustrates how the PMRs would be defined if categories 4 and 5 (with zero study deaths) were combined with category 3; note that the PMRs for categories 1 and 2 are correctly unchanged and that the PMR for category 3–5 (0.42) is simply a weighted average of the original three PMRs (1.67, 0, and 0). However, this combined PMR cannot be compared to the PMRs calculated using Zhou's proposed method, for which categories 4 and 5 would be

Table I. Example calculation of the usual proportionate mortality ratio (PMR) and Zhou's proposed adjusted PMR.

Cause	Study deaths	Referent deaths	Usual PMR	Zhou's proposed PMR
1	10 (1/3)	1000 (1/15)	(1/3)/(1/15) = 5	(1/3)/(1/6) = 2
2	10 (1/3)	2000 (2/15)	(1/3)/(2/15) = 2.5	(1/3)/(2/6) = 1
3	10 (1/3)	3000 (3/15)	(1/3)/(3/15) = 1.67	(1/3)/(3/6) = 0.67
4	0	4000 (4/15)	(0)/(4/15) = 0	Not defined
5	0	5000 (5/15)	(0)/(5/15) = 0	Not defined

Table II. Example calculation of the usual proportionate mortality ratio (PMR) when causes with 0 deaths are combined with cause 3.

Cause	Study deaths	Referent deaths	Usual PMR
1	10 (1/3)	1000 (1/15)	(1/3)/(1/15) = 5
2	10 (1/3)	2000 (2/15)	(1/3)/(2/15) = 2.5
3–5	10 (1/3)	12000 (12/15)	(1/3)/(12/15) = 0.42

undefined. This example illustrates the logical fallacy of the proposal by Zhou (2014) to exclude categories with zero deaths in defining the PMR cause-of-death categories: Combining categories should not lead to changes in the PMRs for other categories.

Second, Zhou also reported the results of a statistical simulation that purports to provide evidence of 'bias' in the usual PMR; however, we contend that his methods are not an appropriate way to evaluate bias. To evaluate bias in a statistical method using statistical simulation, one should generate population data for which the population parameter is known and evaluate the distribution of the sample statistic in repeated sampling from the population. We performed a simulation using SAS (version 9.3, SAS Institute Inc., Cary, NC, USA) to evaluate the performance of the PMR when there are few decedents relative to the number of causes of death. First, we generated a very large standard population of 10 million deaths for which there were 46 causes of death assigned as follows: Cause 1 ($p = 0.25$), causes 2–3 ($p = 0.10$ each), causes 4–6 ($p = 0.05$ each), causes 7–16 ($p = 0.02$ each), causes 17–26 ($p = 0.01$ each), and causes 27–46 ($p = 0.005$ each). Next, we generated small samples of decedents of size $n = 128$ and assigned causes of death using the same distribution. Thus, with 128 decedents and 46 causes of death (ratio = 2.8) the ratio of decedents to causes was similar to the ratio (328/119 = 2.8) observed in a small study (Gibb et al. 2013) used as an example by Zhou for his simulation. Note that with a sample this small, we would expect to rarely observe zero deaths for the more common causes (1, 2 and 3), occasionally observe zero deaths for the not-as-common causes (4–6 and 7–16), and frequently observe zero deaths for the other, rarer,

Table III. Proportionate mortality ratio (PMR) results of the simulation of 10,000 samples of 128 decedents assigned to 46 causes of death.

Population proportion			Usual PMR			Zhou's proposed PMR			Ratio Zhou to Usual	
	Cause	No. zero	No.	Mean	Capture[a]	No.	Mean	Capture	No.	Mean
0.25	1	0	10000	0.999	0.986	10000	0.903	0.958	10000	0.904
0.10	2	0	10000	1.001	0.975	10000	0.904	0.967	10000	0.904
	3	0	10000	0.996	0.976	10000	0.900	0.968	10000	0.904
0.05	4	12	10000	1.005	0.978	9988	0.909	0.981	9988	0.905
	5	10	10000	0.997	0.976	9990	0.902	0.976	9990	0.905
	6	15	10000	1.006	0.973	9985	0.911	0.978	9985	0.905
0.02	7	732	10000	1.001	0.986	9268	0.978	0.993	9268	0.906
	8	727	10000	1.008	0.984	9273	0.984	0.990	9273	0.906
	9	739	10000	1.005	0.985	9261	0.982	0.991	9261	0.906
	...[b]									
0.01	17	2776	10000	1.002	0.990	7224	1.258	0.985	7224	0.907
	18	2792	10000	1.008	0.991	7208	1.268	0.987	7208	0.907
	19	2718	10000	1.001	0.991	7282	1.246	0.988	7282	0.907
0.005	27	5298	10000	0.989	0.995	4702	1.907	0.989	4702	0.907
	28	5222	10000	1.001	0.996	4778	1.899	0.992	4778	0.906
	29	5189	10000	1.019	0.997	4811	1.920	0.993	4811	0.906
	...									

[a]Fraction of samples for which the 95% confidence interval contained the true PMR (1). [b]Results (not shown) for causes 10–16, 20–26, and 30–46 were similar to those presented for causes 7–9, 17–19, and 27–29, respectively.

causes (17–46). Each sample of 128 dece dents was analyzed twice: (i) To evaluate the usual PMR, we computed 46 cause-specific PMRs and assigned PMR = 0 if the particular cause had zero observed deaths, and (ii) to evaluate Zhou's 'adjusted PMR, we computed cause-specific PMRs for causes with 1 or more deaths by ignoring deaths in the standard population for any cause with zero deaths in the sample. For the simulation, we generated 10,000 samples of size $n = 128$ and summarized the resulting PMRs. Because we assigned causes of death to the sample using the same distribution as the standard population, we expected that, on average, each cause-specific PMR would be 1. Systematic differences from 1 would indicate bias.

Our results, summarized in Table III, include, for each cause of death category, the number of samples with zero observed deaths. For the usual method, the table includes the sample size, the mean PMR, and the fraction of samples that 'capture' the true PMR (i.e., the fraction of samples for which the 95% confidence interval contains the true value of 1). Similar statistics are provided for Zhou's proposed method. The final column includes the mean ratio of Zhou's method to the usual method (which is only computed when both methods are defined – that is, when the number of deaths is positive). As expected, for causes 1–3 (fairly common causes of death), there were no samples with zero deaths, but for the rare causes of death (27–46) more than half of the samples had zero deaths. For the usual method, the sample size is always 10,000 because when the usual method observes no deaths for a particular cause it assigns PMR = 0. Because Zhou's method does not assign a PMR when the number of deaths is zero, the sample size is less than 10,000 for rarer causes. The mean PMR for the usual method is around 1 for all causes of death – this is what we expected to see if the method produced no bias. The mean PMR for the Zhou method, however, was < 1 (i.e., downwardly biased) for causes 1–6 (for which no 'zero deaths' occurred) – this is the key to understanding that Zhou's proposed method is biased. Also, the mean PMR for the Zhou method was >1 for causes 17–26 and 27–46 (for which zero deaths were quite common) – this seems counterintuitive because Zhou's method will always produce a PMR that is less than the usual PMR (Zhou provides the algebra to show that this is the case) but the usual method assigns PMR = 0 when there are zero deaths and Zhou's method is undefined when there are zero deaths. The mean ratio of the Zhou method, when defined, to the usual method is always less than one.

The PMR methodology is not without limitations (Checkoway et al. 1989). PMR estimates depend on values in adjacent categories, as an excess in one must be offset by a deficit in another. When using small study groups with large numbers of categories, confidence intervals are very wide, indicat ing that parameters are poorly estimated, and PMRs may frequently be zero; however, there is no evidence that these PMRs are biased. An approach that can be used to minimize the number of 'zero' PMRs may be to combine categories into larger groupings (e.g., all cancers; all circulatory diseases). Until Zhou (2014), we are not aware that anyone has advo cated performing an analysis using only death categories that appear among the decedents. Here, Zhou is advocating, after looking at the data, only considering outcomes with positive counts, but he is not taking into account the "conditional" nature of his procedure. We suggest that doing so introduces a downward bias in PMR estimates.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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