

This is a version of a comment submitted on ASA Connect on March 15, 2017, in a response to a request for comments by American Statistical Association Science Policy Director Steve Pierson regarding a document on common errors in biomedical research. Numbers have been added to paragraphs to facilitate reference to particular points.

1. This comment involves the guidance's apparent approbation of the risk ratio reflected in the listing of the following thing to be avoided: "Reporting approximate risk ratios from a logistic regression, or interpreting odds ratios as risk ratios, instead of just estimating the risk ratios in a log-binomial model."

2. The problematic nature of the risk ratio as a measure of association is the subject I recently treated in an October 8, 2015 letter to the American Statistical Association (at 12-13, 28-29, 34)[1] November 14, 2016 comment to the Commission on Evidence-Based Policymaking (CEBP) (at 41-42), [2] and a November 2015 seminar at the University of Massachusetts School of Medicine (UMMS) (slides 70-79),[3] as well as in comments on subgroup effect guidelines of the Federal Drug Administration (May 2014) [4] and the European Medicines Agency (July 2014).[5] It is most extensively treated in my Subgroup Effects web page,[6] though that page has not been recently updated.

3. A principal reason that risk ratio is the most common measure of association in biomedical research and elsewhere is the belief that it will tend to be constant across different baseline rates (at least absent a subgroup effect as the concept is generally understood).

Correspondingly, departure from a constant relative effect is the standard benchmark for identifying a subgroup effect.

4. But there are fundamental problems with the assumption that risk ratio is constant across different baseline rates and these problems also go to the utility of the risk ratio as a measure of association. The problems involve the following related, but not necessarily congruent, issues: (a) there are reasons to expect that (in the case of two groups) a factor that affects an outcome rate will tend to show a larger relative effect on the outcome for the group with the lower baseline rate for the outcome while showing a larger relative effect on the opposite outcome for the other group; (b) in point of fact one commonly observes the pattern described in (a) (and it may exist in the overwhelming majority of cases at least where baseline rates differ substantially); (c) irrespective of (a) and (b), it is illogical to expect a factor to cause equal proportionate changes on rates of experiencing an outcome for two groups with different baseline rates for the outcome, given that it is not possible for a factor to do so while at the same time causing equal proportionate changes in rates of experiencing the opposite outcome; (d) (a variation of (c)) anytime one finds that a factor causes equal proportionate changes for different baseline rates of experiencing an outcome one will necessarily find that the factor causes unequal proportionate changes for rates of experiencing the opposite outcome; and (e) it is illogical to regard a particular risk ratio as reflecting the same level of association with respect to different baseline rates for an outcome, since if it does, the risk ratio for the opposite outcome will necessarily show different strengths of association in the two cases.

5. In "Divining Difference," *Chance* (Fall 1994), [7] I first explained the reasons to expect that a factor that affects an outcome rate will tend to show a larger relative effect on the outcome for the group with the lower baseline rate for the outcome while showing a larger relative effect on the opposite outcome for the other group. I have since identified a variety of situations, cast

in terms of subgroup effects, where one will reach an opposite conclusions about such effect depending on whether one examines the relative effect on a favorable outcome or the relative effect on the adverse outcome. See, e.g., my 2009 JSM presentation,[8-10] Table 7 of "Race and Mortality Revisited," Society (July/Aug. 2014), [11,12] and Tables 10-12 of my 2013 Federal Committee on Statistical Methodology paper.[13]

6. But I have also identified scores or hundreds of situation of where one reaches opposite conclusions about whether a demographic difference is larger in one setting than another or whether such difference has increased or decreased over time depending on whether one examines relative differences in the favorable outcome or relative differences in the corresponding adverse outcomes. All such situations necessarily also reflect situations where one would reach a different conclusion about the comparative size of an effect depending on whether one examines the relative effect/change as to the favorable outcome or the relative effect/change as to the adverse outcome. That is, for example, Table 6 of my 2008 Helsinki presentation [14] shows the way that relative differences between mortality rates of Finnish home owners and renters decrease with age while relative differences between the survival rates of such groups increase with age. The table is necessarily also showing that the relative negative effect of being a renter (positive effects of being an owner) on mortality decreases with age while the corresponding relative negative effect on survival increases with age. See also my Life Tables Illustrations page.[15]

7. Further, every situation where others have observed that one reaches an opposite conclusions about the comparative size of an effect or the direction of change in a demographic difference depending on whether one examines the effect/difference in relative terms or in absolute terms necessarily also involves a situation where one would reach opposite conclusion depending on which relative difference/effect one is examining. See the November 14, 2016 CEBP comments [2] (at 15 n. 26).

8. It does not matter that one will observe some or many departures from these patterns, as I discuss, among many other places, in the ASA letter [1] (at 27-28). The patterns must be taken into account in appraising the soundness of a measure. Yet, if the matter could be effectively studied, we might well find that the patterns exist in the overwhelming majority of cases where there exist substantial differences in baseline rates.

9. It seems, however, that few people employing risk ratios to appraise effects sizes know that it is even possible for this to happen. Almost 60 years ago, in an important New England Journal of Medicine article titled "Shall We Count the Living or the Dead" (*N Engl J Med* 1958; 259:1210-14), Mindel C. Sheps noticed that a situation reflecting the largest relative gender effect on mortality also showed the smallest relative gender effect on survival. I have discussed in an October 9, 2012 letter to Harvard University [16] (at 11-12) and the UMMS seminar [3] (slides 52-56) that Professor Sheps unfortunately regarded this situation as reflecting the absence of a pattern rather than as an indication of a pattern (or as a pattern itself). But, to my knowledge, no published work has since reflected an awareness that it is possible to reach opposite conclusions about the comparative size of an effect depending on whether one examines relative effects/differences as to mortality or relative effects/differences as to survival (save in places I have noted the pattern or where it has been recognized by others responding to my work). The same holds for every other combination of adverse and corresponding favorable outcomes.

10. The situation is especially noteworthy with regard to cancer outcomes. For observers commonly refer to relative differences/effects as to survival and as to mortality interchangeably, often stating they are examining the former while in fact examining the latter. Invariably they do so without recognizing that one may or commonly would (or in fact would in the particular study) reach opposite conclusions depending on whether one examines mortality or survival. See my Mortality and Survival page[17,18] (though it has not been recently updated). See also my November 28, 2016 CEBP comments [19] (at 1-2) regarding a very recent study. And see my comments on Yu BMJ Cancer 2009,[20] Cornell PLoS Medicine 2012,[21] Kravdal BMC Public Health 2011,[22] Hockey Emerging Themes in Epidemiology 2011[23], and Muenning Health Affairs 201.[24]1

11. The above paragraphs address the issues initially summarized as (a) and (b). The (c) to (e) issues, which exist irrespective of (a) and (b), are effectively stated above. They are also addressed more specifically in the above-mentioned Subgroup Effects page,[6] and in various points in the ASA letter and the CEBP comments. See also the Subgroup Effects – Nonclinical,[25] Illogical Premises,[26] Illogical Premises II,[27] and Inevitability of Interaction[28] pages (which are summarized at page 42-43 of the November 14, 2016 CEBP comments[2]). And see the comments on Hingorani BMJ 2013[29] and Altman BMJ 2003.[30] The other comments listed at page 43 of the November 14, 2016 CEBP comments vary in their focus on (a) and (b) versus (c) through (e). The emphasis in a number of items, and especially the Subgroups Effects page, is on the employment of the risk reduction observed in a clinical trial in order to calculate the absolute risk reduction and associate number-needed-to-treat in circumstances involving baseline rates different from that in the trial.

12. The following should be borne in mind in considering all of the above points. The forces that cause two favorable outcome rates to differ (or, otherwise put, the effect of a factor on those rates) are exactly the same as the forces that cause the corresponding adverse outcome rates to differ. Thus, I suggest, it would be a mistake to think that a measure that is saying that forces are stronger as to the favorable outcome in setting A than setting B but stronger as to the adverse outcome in setting B than setting A (or that the forces are growing strong as to the favorable outcome but weaker as to the adverse outcome) could be saying something is statistically sound.

13. Some observers would maintain that the odds ratio satisfactorily addresses issues I raise about ways measures tend to be affected by the prevalence of an outcome. I don't think that is correct, as reflected in my illustrations of the ways odds ratios tend to be affected by an outcome and as discussed, say, at page 22 note 14 of my September 12, 2016 letter to the Antioch School District[31]. But usually the odds ratio will not result in the estimation of the number-needed-to-treat that is substantially different from that estimated according to what I suggest is the preferred method. See Tables 3 and 4 of the Subgroup Effects page[6]. See also the comment on Wang Emerging Themes in Epidemiology 2009.[32] And certainly, depending on the nature of the underlying distributions, in some case the odds ratio could be a superior measure to the one I suggest.

14. Thus, let us assume that the odds ratio is indeed the preferred approach. The guidance is steering the user away from the odds ratio toward the risk ratio, which typically means the risk ratio the observer happens to be looking at (usually unaware of the possibility or likelihood that the risk ratio for the opposite could yield substantially different results). Thus, I suggest, guidance promoting the odds ratio over the risk ratio would be superior to guidance promoting the risk ratio over the odds ratio, even if such guidance fails to address issues about the ways

measure tend to be affected by the prevalence in a manner I have suggested be done in my letter to ASA and my CEBP comments.

15. Finally, I call your attention to a recent paper by Huijtfelt et al. (“The Choice of Effect Measure for Binary Outcomes: Introducing Counterfactual Outcome State Transition Parameters” (2016)).[33] It also challenges the assumption of a constant risk ratio across different baseline rates but from a perspective rather different from mine.

1. http://jpscanlan.com/images/Letter_to_American_Statistical_Association_Oct._8,_2015_.pdf
2. http://www.jpscanlan.com/images/Comments_of_J_Scanlan_for_Comm_on_Evidence-Based_Policymaking_Nov._14,_2016_.pdf
3. http://jpscanlan.com/images/Univ_Mass_Medical_School_Seminar_Nov._18,_2015_.pdf
4. http://jpscanlan.com/images/Comment_on_FDA_Subgroup_Regulations_.pdf
5. http://jpscanlan.com/images/Comment_on_EMA_Subgroup_Guidelines_.pdf
6. <http://www.jpscanlan.com/scanlansrule/subgroupeffects.html>
7. http://jpscanlan.com/images/Divining_Difference.pdf
8. http://www.amstat.org/meetings/jsm/2009/onlineprogram/index.cfm?fuseaction=abstract_details&abstractid=304941
9. http://www.jpscanlan.com/images/Scanlan_JSM_2009.ppt
10. http://www.jpscanlan.com/images/JSM_2009_ORAL.pdf
11. http://jpscanlan.com/images/Race_and_Mortality_Revisited.pdf
12. <http://link.springer.com/article/10.1007%2Fs10888-014-9289-4#page-1>
13. http://jpscanlan.com/images/2013_Fed_Comm_on_Stat_Meth_paper.pdf
14. http://jpscanlan.com/images/Scanlan_JP_NDS_Presentation_2R.ppt
15. <http://jpscanlan.com/scanlansrule/lifetableillustrations.html>
16. http://jpscanlan.com/images/Harvard_et_al._Commissioned_Paper_Letter.pdf
17. <http://jpscanlan.com/mortalityandsurvival2.html>
18. http://www.jpscanlan.com/images/Mortality_and_Survival.pdf
19. http://jpscanlan.com/images/Comments_for_the_Commission_on_Evidence-Based_Policymaking_Nov._28,_2016_.pdf
20. <http://www.biomedcentral.com/1471-2407/9/364/comments#1563696>
21. <http://www.plosmedicine.org/annotation/listThread.action?inReplyTo=54807&root=54807>
22. <http://www.biomedcentral.com/1471-2458/11/804/comments#730697>
23. <http://www.ete-online.com/content/8/1/3/comments>
24. <http://content.healthaffairs.org/cgi/eletters/hlthaff.2010.0073v1#454605>
25. <http://jpscanlan.com/scanlansrule/subgroupeffectsn.html>
26. <http://jpscanlan.com/scanlansrule/illogicalpremises.html>
27. <http://jpscanlan.com/scanlansrule/illogicalpremisesii.html>
28. <http://jpscanlan.com/scanlansrule/inevitableinteraction.html>
29. <http://www.BMJ.com/content/346/BMJ.e5793/rr/632884>
30. <http://www.BMJ.com/content/326/7382/219?tab=responses>
31. http://www.jpscanlan.com/images/Letter_to_Antioch_Unified_School_District_Sept._12,_2016_.pdf
32. <http://www.ete-online.com/content/6/1/1/comments>
33. <https://arxiv.org/abs/1610.00069>

