Reviewer's report

Title: Adverse Childhood Experiences are Associated with the Risk of Lung Cancer: A Prospective Cohort Study

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Reviewer: Steven D Stellman

Reviewer's report:


This article was previously reviewed by three reviewers, revised by the authors, and re-submitted with a lengthy cover letter. All three reviewers approved the article for publication, albeit with various comments and qualifications. My assignment was to advise the Editor whether the article is appropriate for BMC Medicine or whether it should be sent to the more narrowly focused journal BMC Public Health.

In my opinion the paper should be published in BMC Public Health. While I have a number of misgivings (see comments below), I do not intend to second-guess the three reviewers who have done a thorough job. However, I hope the Editor will bring these additional comments to the authors’ attention.

This study assesses the risk of incident or fatal lung cancer in relation to "adverse childhood experiences" (ACE) in a cohort of over 17,000 San Diego Kaiser HMO members. The main conclusion is that ACE may be an independent risk factor for lung cancer. It is an intriguing hypothesis. There are very few prior studies of this possible relationship. One very weak Canadian study has just appeared in the ACS journal Cancer (Thomson 2009), and is based on a cross-sectional analysis in which the “exposure” is self-reported childhood abuse and the outcome is any self-reported cancer. The present study is much stronger: it is longitudinal and is based on an extensive ACE questionnaire and actual hospital records or an NDI match.

The baseline population is 17,337 Kaiser members who completed medical exams at San Diego Health Appraisal Clinic in two waves, 1995-7. ACE data were gathered by mailed questionnaire sent 2 weeks after medical exam. ACE questionnaire is referred to the subject’s experience up to age 18. For modeling purposes, a summary score with integer values 0-6 is used as the independent variable.

The graded associations (i.e., dose-responses) are undoubtedly correct – an association between ACE and adult lung cancer clearly exists. Given the higher prevalence of smoking in all eight components of the ACE scale (Table 1), it
could scarcely be otherwise. The central issue of this paper is whether this
association holds independently of cigarette smoking, or whether it can be
explained completely or in part by smoking. The authors use appropriately
cautious language in their Conclusions (“MAY be associated … MAY only be
partly explained). However, I am not fully convinced that they have made their
case even to this cautious extent.

The authors argue with Reviewer 1 regarding their treatment of smoking as a
causal intermediate variable. Treatment of potential mediators is a very
troublesome exercise and there is considerable disagreement among
epidemiologists about the correct approach. Many social scientists and
psychiatric epidemiologists prefer latent variable analysis (path analysis) or SEM.
A more recent approach uses directed acyclic graphs. A regression approach
advocated by MacKinnon uses the paradigm:

\[ Y = c X + e_1 \]
\[ M = a X + e_2 \]
\[ Y = c' X + bM + e_3 \]

The independent variable \( X \) causes the outcome variable \( Y \)
The independent variable \( X \) causes the mediator variable \( M \)
The mediator \( M \) causes the outcome variable \( Y \) when controlling for the
independent variable \( X \). This must be true. If the effect of \( X \) on \( Y \) is zero when
the mediator is included \( (c' = 0) \), there is evidence for mediation (Judd & Kenny,
1981a, 1981b). This would be full mediation. If the effect of \( X \) on \( Y \) is reduced
when the mediator is included \( (c' < c) \), then the direct effect is said to be partially
mediated.

From: http://www.public.asu.edu/~davidpm/ripl/q&a.htm

Brown et al. take the much simpler route of adjusting for smoking as if it were a
confounder (Figure 2, Model B) and argue that ACE must make at least some
independent contribution to lung cancer risk because the RR’s for the higher
exposure strata remain statistically significant. This is a very weak and
unconvincing approach, especially for these data. Figure 2 presents ACE-specific
lung cancer risk (incidence study) with risk predicted by 2 models. Model A
adjusts for 6 socio-demographic variables. Model B is Model A plus adjustment
for subject smoking and parental smoking, and shows substantial attenuation of
risks, e.g., by one-third in the highest category. The authors stake their case for
an independent ACE effect on this incomplete attenuation. However, the same
Figure also contains a table of lung cancer risk by smoking. Besides the
expected powerful effect of smoking, it shows that the magnitude of the RR for
current smokers of 1 or more packs per day is more than an order of magnitude
greater than the lung cancer risk in the highest ACE category in Model B. It is
very difficult to distinguish ACE signal from noise in the environment of a 10-fold
larger smoking effect.

There are other ample opportunities for artifacts or misleading findings. Table A1
shows that the vast majority (75%) of subjects with high ACE scores (6, 7, or 8) were under age 55. This is relevant to the statement on p. 12 that “As the ACE Score increased, the adjusted mean age at incident hospitalization for lung cancer decreased (P for trend <0.001) (Figure 3). Persons with 6 or more ACEs were hospitalized nearly 20 years earlier on average than those without ACEs (60.7 years; 95%CI=49.2-72.3 v 73.8 years; 95%CI=70.3-77.4).” In the first place, the average difference is 13.1 years, which is not “20 years earlier.” More importantly, age at death reflects nothing more than age at life, and it is not surprising that a young exposed group has a young age death (K Rothman, AJPH 1992; 82:761). I would not regard this observation as worth reporting, let alone devoting an entire Figure to (Fig. 3).

The attributable risk calculations are also not very interesting. They provide no additional information that is not already present in the risk calculations, and are best used for heuristic or educational purposes. Attributable risk is a tenuous concept that relies on a great many simplifications even for a single risk factor, and application to two or more risk factors simultaneously is an even bigger stretch. Even the authors back-pedal on this point somewhat in their penultimate paragraph (p. 19).

I agree with the reviewer who stated that the relative risk functions in Figure 2 are superfluous.