Risk Factors for Disease Risk Factors and Attributable Risk Calculations: Are There Mathematical Limits?

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LETTER TO THE EDITOR

The Adverse Childhood Experiences (ACE) Study, a collaborative effort between Kaiser Permanente (San Diego, CA) and the Centers for Disease Control and Prevention (Atlanta, GA), was designed to examine the long-term relationship between adverse childhood experiences (ACEs) and a variety of health behaviors and outcomes in adulthood [1]. ACEs include childhood emotional, physical, or sexual abuse and household dysfunction during childhood. The ACE Study, based on chronic disease prevention and control models, proposes that ACEs influence social, emotional, and cognitive impairments which in turn increase the probability of adopting health risk behaviors that have been documented to influence the subsequent development of disease, disability, social problems, and ultimately premature death. We use the ACE pyramid to depict this concept (see www.cdc.gov/nccdphp/ace/pyramid.htm).

Prior ACE Study results demonstrate that an integer count (the ACE Score) of the number of categories of ACEs has a strong, graded relationship to a wide variety of health and social problems from adolescence to adulthood [2, 3]. Thus, ACEs may act as a "risk factor for risk factors" that increase the probability of disease.

In the process of examining the potential effects of ACEs on health outcomes, we realized there are apparent mathematical limits to the proportion of disease one can expect to attribute to ACEs when they act as a risk factor for a risk factor in a causal chain. To be clear in terminology, we consider risk factors to be characteristics, traits, lifestyle behaviors or habits that increase the probability of disease, or more generally, of some adverse outcome [4]. Because ACEs are a risk factor for smoking [5], we were interested in determining the fraction of smoking-attributable lung cancer that could be ascribed to ACEs. We proceeded by multiplying two attributable risk percent (AR%) values: the AR% for exposure to ACEs on smoking and the AR% for smoking on lung cancer.

We calculated the AR% as the ratio of the difference in risk between exposed and non-exposed divided by the risk in the exposed or alternatively relative risk (RR) – 1 divided by the RR ($AR\% = \left(\frac{RR-1}{RR}\right)\times 100\%$). Of course, the AR% represents the proportion of disease among exposed persons that is due to the exposure; that is to say, assuming a causal relationship, if we were to remove the exposure of interest we could reduce the risk of disease by an amount equal to the AR% [6].

In the ACE Study data, approximately 85%-95% of lung cancer (identified prospectively through hospital discharge records or mortality records) among smokers is attributable to smoking, depending on whether one assesses the risk for ever smokers (RR=7.01, 95%CI=4.13-11.89) or current smokers (RR=19.65, 95%CI=10.76-35.87) (RRs adjusted for age, sex, race/ethnicity, education) [7].

The adjusted relative odds of ever smoking or current smoking associated with exposure to ACEs are shown in the Table **1**. AR% values range from 26% for current smoking among persons exposed to ≥1 ACEs and 69% for ever smoking among persons exposed to ≥6 ACEs [5]. Assuming that 1) smoking is causally related to lung cancer, 2) 90% of lung cancer is attributable to smoking, and 3) ACEs are a causal risk factor for smoking, our multiplication of proportions for any ACE and for ≥6 ACEs (90%×26%; 90%×39%; 90%×52%; 90%×69%) resulted in an estimated 23% to 62% of smoking-attributable lung cancer depending on smoking exposure and exposure to ACEs.

Multiplying two proper fractions (i.e., where the numerator is less than its denominator) always results in a smaller fraction unless the fractions are both of the value zero (0) or one (1). A cursory review of the arithmetic suggests that attaining large AR% values for the distal risk factor in the chain requires that the AR% values for each risk factor considered must be "large" in value, or alternatively close to 1. As a result, there are apparent limits to the proportional amount of an outcome that can be explained by ACEs under the ACE model.

We are unaware of any literature that has examined the possible mathematical limits of AR% when considering risk factors for risk factors for disease or health outcomes. We welcome comments and critique and would very much like to see a formal presentation on this topic, since the consideration of risk factors for risk factors and disease has important implications for chronic, non-communicable disease prevention.

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Table 1. Association Between Number of Adverse Childhood Experiences (ACEs) and Smoking

	Ever Smoker OR (95%CI)*	AR%	Current Smoker OR (95%CI)*	AR%
ACE Score				
0	1.00 (referent)		1.00 (referent)	
1	1.29 (1.19-1.40)	22	1.10 (0.95-1.28)	9
2	1.62 (1.47-1.78)	38	1.28 (1.09-1.52)	22
3	1.91 (1.70-2.14)	48	1.60 (1.33-1.93)	38
4 or 5	2.44 (2.17-2.74)	59	1.78 (1.49-2.13)	44
6, 7, or 8	3.27 (2.67-4.01)	69	2.08 (1.59-2.72)	52
ACE Score				
0	1.00 (referent)		1.00 (referent)	
$\geq$1	1.63 (1.52-1.74)	39	1.36 (1.20-1.54)	26

OR, odds ratio; CI, confidence interval; AR%, attributable risk percent.
ORs adjusted for age, sex, race/ethnicity, education.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the authors' affiliated institutions.

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Received: July 22, 2009 Revised: November 11, 2009 Accepted: November 16, 2009