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Are major behavioral and sociodemographic risk factors for mortality additive or multiplicative in their effects?

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ABSTRACT

All individuals are subject to multiple risk factors for mortality. In this paper, we consider the nature of interactions between certain major sociodemographic and behavioral risk factors associated with all-cause mortality in the United States. We develop the formal logic pertaining to two forms of interaction between risk factors, additive and multiplicative relations.

We then consider the general circumstances in which additive or multiplicative relations might be expected. We argue that expectations about interactions among socio-demographic variables, and their relation to behavioral variables, have been stated in terms of additivity. However, the statistical models typically used to estimate the relation between risk factors and mortality assume that risk factors act multiplicatively.

We examine empirically the nature of interactions among five major risk factors associated with all-cause mortality: smoking, obesity, race, sex, and educational attainment. Data were drawn from the cross-sectional NHANES III (1988–1994) and NHANES 1999–2010 surveys, linked to death records through December 31, 2011. Our analytic sample comprised 35,604 respondents and 5369 deaths.

We find that obesity is additive with each of the remaining four variables. We speculate that its additivity is a reflection of the fact that obese status is generally achieved later in life. For all pairings of socio-demographic variables, risks are multiplicative. For survival chances, it is much more dangerous to be poorly educated if you are black or if you are male. And it is much riskier to be a male if you are black. These traits, established at birth or during childhood, literally result in deadly combinations.

We conclude that the identification of interactions among risk factors can cast valuable light on the nature of the process being studied. It also has public health implications by identifying especially vulnerable groups and by properly identifying the proportion of deaths attributable to a risk factor.

1. Introduction

All individuals are subject to multiple risk factors for mortality at any given time. These risk factors may interact with one another in a variety of ways that contribute to one's risk of dying. In this paper, we consider the nature of interactions between major risk factors associated with all-cause mortality. We focus on two forms of interaction between risk factors, additive and multiplicative relations. We then consider the circumstances in which additive or multiplicative relations might be expected. In an exploratory analysis, we examine the nature of interactions between certain major behavioral and sociodemographic risk factors associated with all-cause mortality among middle-aged and older Americans. We explicitly ask whether the risks are additive in their effects, multiplicative, or whether they interact in some other fashion. Our principal goal is to highlight the importance of this often neglected issue in interpreting data on mortality.

2. Background

In studies of mortality, researchers often consider multiple risk factors jointly in statistical models. The risk factors assessed take a wide variety of forms including those that are demographic, behavioral, biological, or environmental in nature. It is not unusual to include risk factors that are drawn from two or more of these different domains. For example, studies of behavioral risk factors

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such as smoking often control for socio-demographic attributes such as sex and social class. Cox hazard models or logistic regression models are most often implemented to investigate these multivariate processes. Such models typically make the assumption that risk factors are multiplicative in their effects (Andersson et al., 2005). Rarely is this assumption tested or even acknowledged.

We believe that the identification of the nature of interactions among risk factors can cast valuable light on the nature of the process being studied. It may also have public health implications by identifying especially vulnerable groups and by properly identifying the proportion of deaths attributable to a risk factor.

The terminology for considering statistical interactions between variables is somewhat unsettled. Here we follow the terminology and concepts employed in an extensive review paper by VanderWeele and Knol (2014). Many forms of interaction might exist between variables, each of them expressible mathematically. We focus in this paper on the two simplest forms of interaction, those typically termed “additive” and “multiplicative”. What we mean by these terms is best illustrated algebraically. We develop an example using two major risk factors, smoking and obesity, which are treated as dichotomous variables.

Notation.

$\mu^{\overline{OS}}$ = Death rate of non-obese, non-smokers
$\mu^{O\overline{S}}$ = Death rate of obese non-smokers
$\mu^{\overline{O}S}$ = Death rate of non-obese smokers
μ^{OS} = Death rate of obese smokers

The relative risk of death from obesity among non-smokers is k, so that

$$\mu^{O\overline{S}} = k\mu^{\overline{OS}}$$

The relative risk of death from smoking among the non-obese is j, so that

$$\mu^{\overline{O}S} = j\mu^{\overline{OS}}$$

If the risks of death associated with obesity and smoking are additive, then

$$\mu^{OS} = \mu^{\overline{OS}} + \left(k\mu^{\overline{OS}} - \mu^{\overline{OS}}\right) + \left(j\mu^{\overline{OS}} - \mu^{\overline{OS}}\right) = \mu^{\overline{OS}}(k + j - 1)$$

Dividing all death rates by the death rate of non-obese non-smokers, $\mu^{\overline{OS}}$, produces the set of relative risks shown in Table 1 (under a) Additive). Observed values less than $(j + k{-}1)$ in the upper left hand quadrant would be described as sub-additive and values larger than that value would be described as super-additive.

If, on the other hand, the risks are multiplicative, then the value in the upper left quadrant would simply be jk, as shown in Table 1(under b) Multiplicative). Values greater than jk would be considered super-multiplicative and values below jk would be considered sub-multiplicative.

The nature of interactions has direct implications for relative risks. If interactions are multiplicative, then the relative risk of death from one exposure is the same for different values of the other exposure (k in the case of obesity in Table 1b). If interactions are additive, then the relative risks of death from one exposure will depend on the value of the other exposure [k vs. $(j + k{-}1)/j$]. k will be greater than $(j + k{-}1)/j$ as long as k and j are both greater than 1.00. In other words, if additivity prevails, then the relative risk of death associated with obesity will be lower among smokers than among non-smokers. Under additivity, smokers and non-smokers would be equally “vulnerable” or “susceptible” to the effects of obesity, in the sense that being obese adds the same incremental risk of death in the two groups.

If the relative risk of death associated with obesity for smokers is between $(j + k{-}1)/j$ and k, then the risks are between additive and multiplicative (i.e., they are super-additive and sub-multiplicative). In these cases it is reasonable to describe smokers as *more* vulnerable to the hazards of obesity than non-smokers despite the fact that their relative risks of death associated with obesity are lower. Two risks are sometimes described as “synergistic” when the presence of one exposure increases the relative risk associated with the other exposure, even when their joint effect may be sub-multiplicative.

VanderWeele and Knol (2014) refer to the relations defined above as pertaining to interactions “on an additive scale”. An alternative approach is to consider interactions “on a multiplicative scale”. In effect, interactions are considered using the logarithm of risks rather than the risks themselves. Additivity in the logarithms “on the multiplicative scale” translates into multiplicativity of risks “on the additive scale”. VanderWeele and Knol (2014) advocate using an additive scale because of its greater relevance to efforts to improve public health. We prefer it as well for its conceptual clarity. When risks are additive on the additive scale, exposures affect outcomes independently of one another; the impact of one exposure on mortality does not depend on the level of the other exposure. No such test of independence is available on the multiplicative scale.

The statistical methods for the assessment of interactions are well developed (Berrington de González and Cox, 2005; Greenland, 2009). Testing for departures from the multiplicative interactions assumed in logistic regressions or hazard models is straightforward; one needs simply to create and test the significance of a product variable. Li and Chambless (2007) have provided procedures and programming code for testing for the significance of additive interactions in hazard models. Hosmer and Lemeshow (1992) provide significance tests for additive models when logistic regression is used.

The theoretical underpinnings of the concepts are not as clear as the statistical methods for evaluating their strength. What circumstances are expected to produce additive or multiplicative relationships between two risk factors? We provide some preliminary ideas about this issue, partly based on a variety of approaches that have appeared in the literature on mortality and disease incidence.

Additivity. We expect that risk factors will be additive in their effects when they pertain to different, unrelated, disease or injury processes. For example, the excess mortality rates of men engaged in trench warfare should be additive to those of smoking; there is no reason to expect smokers to be more or less protected from the hazards of battle than non-smokers. Using this reasoning, the all-cause mortality risks associated with asbestos exposure should be approximately additive to those of obesity since the risks primarily manifest themselves in different disease processes.

Super-additive relations are more likely to pertain when two risk factors are associated with the same disease process or organ system. For example, damage done to an organ by one exposure could render the organ more vulnerable to damage by another exposure. Asbestos exposure and smoking both affect the risk of

Table 1
Relative risks of death classified by smoking and obesity status.

a) Additive				b) Multiplicative			
		Smoking				Smoking	
		Yes	No			Yes	No
Obese	Yes	$j+k{-}1$	k	Obese	Yes	jk	k
	No	j	1		No	j	1